Why does cancer research focus on treatment, not prevention?

Robert S. Chapkin, Ph.D.

Allen Endowed Chair in Nutrition

Distinguished Professor

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CHAPKIN LAB
PROGRAM IN INTEGRATIVE
NUTRITION & COMPLEX DISEASES

Prevention Advice

Bert Vogelstein is Co-director of the Ludwig Center

… **if the current trends continue, the number of cancer cases diagnosed annually by 2050 is likely to double as a result of population aging. So if we as a society hope to head off the coming storm, we better get more serious about cancer prevention soon.**

Prevention is as good as a cure

Priorities for the US Cancer Moonshot Initiative face an uncertain funding future — but it must not ignore proven prevention programmes in favour of glitzy research.

Cancer prevention: Molecular and epidemiologic consensus

Research in many fields emphasizes the value of prevention

"...cancer death rates could be reduced by 70% around the world, even without the development of any new therapies."

Interception Research

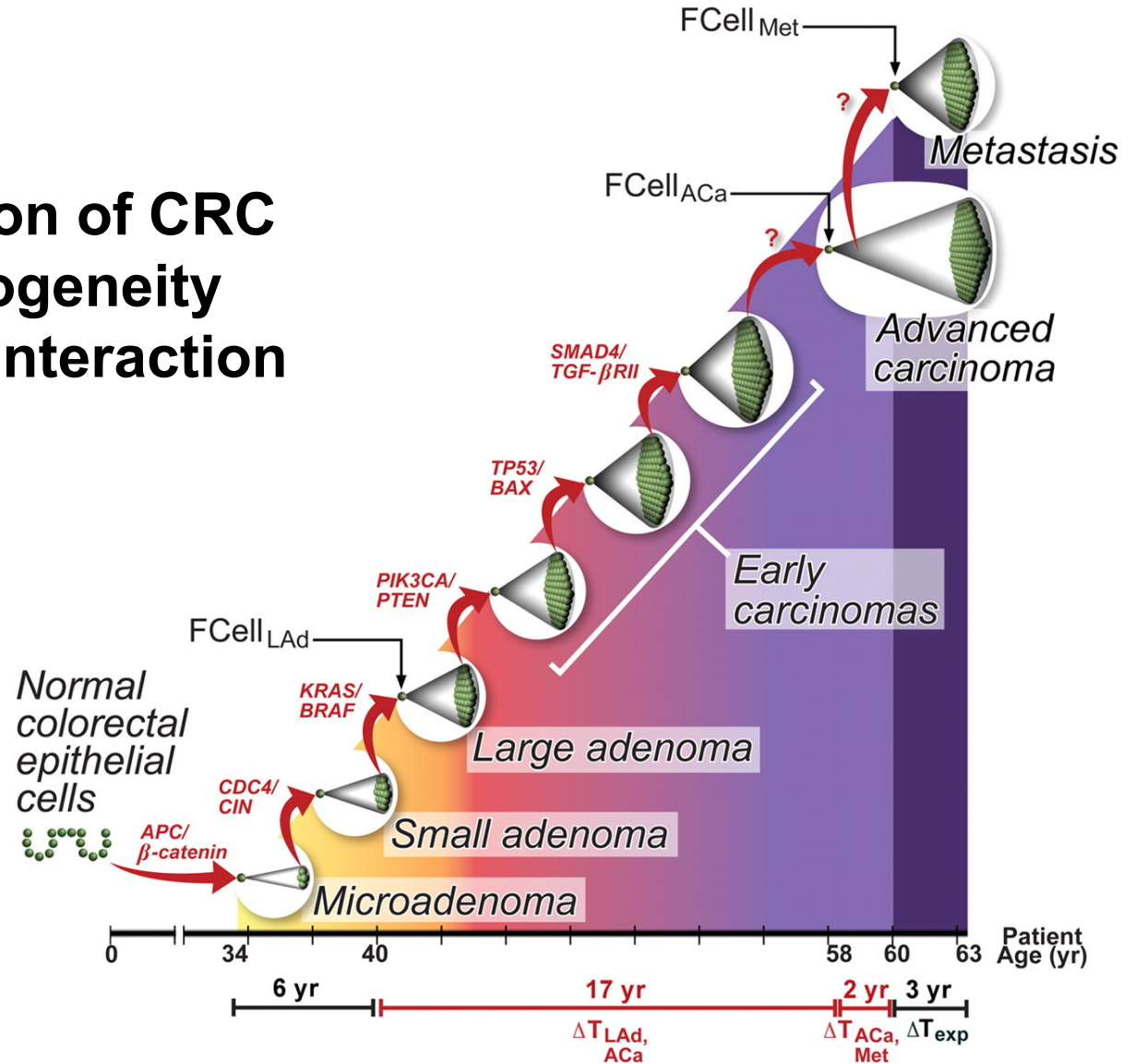✓**Prevention**
✓**Early Detection**
✓**Early Intervention**
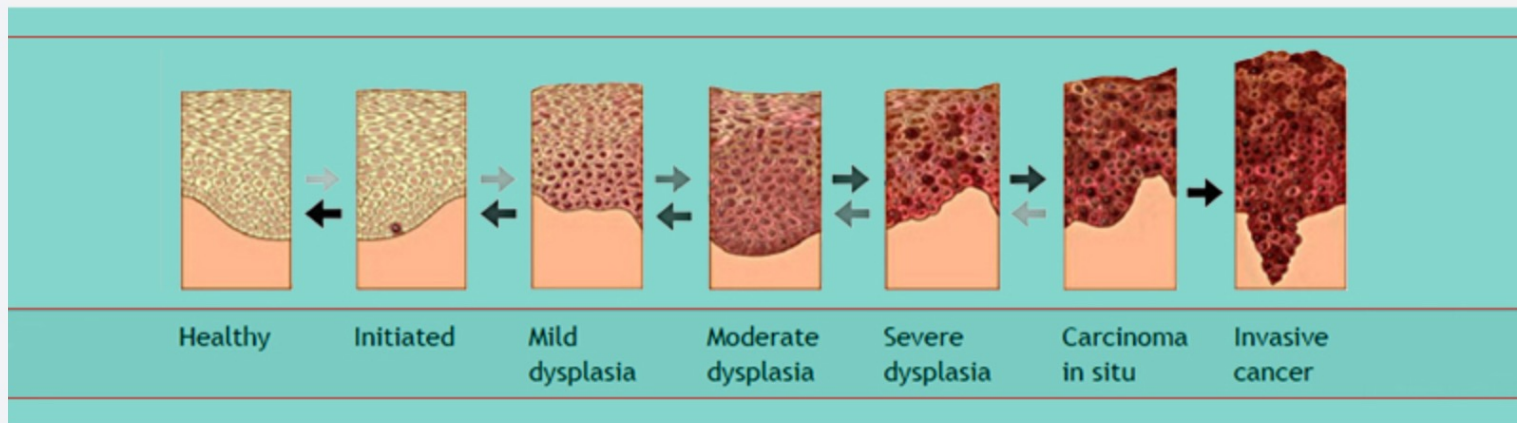
"Molecular basis for dietary chemoprevention"

Song, *Science 361*:1317, 2018

Chemoprevention Challenges

1. Time – evolution of CRC
2. Genetic Heterogeneity
3. Host/Microbe Interaction

Jones S et al. PNAS 2008;105:4283-4288

PNAS

Target the Early Prevention of Cancer
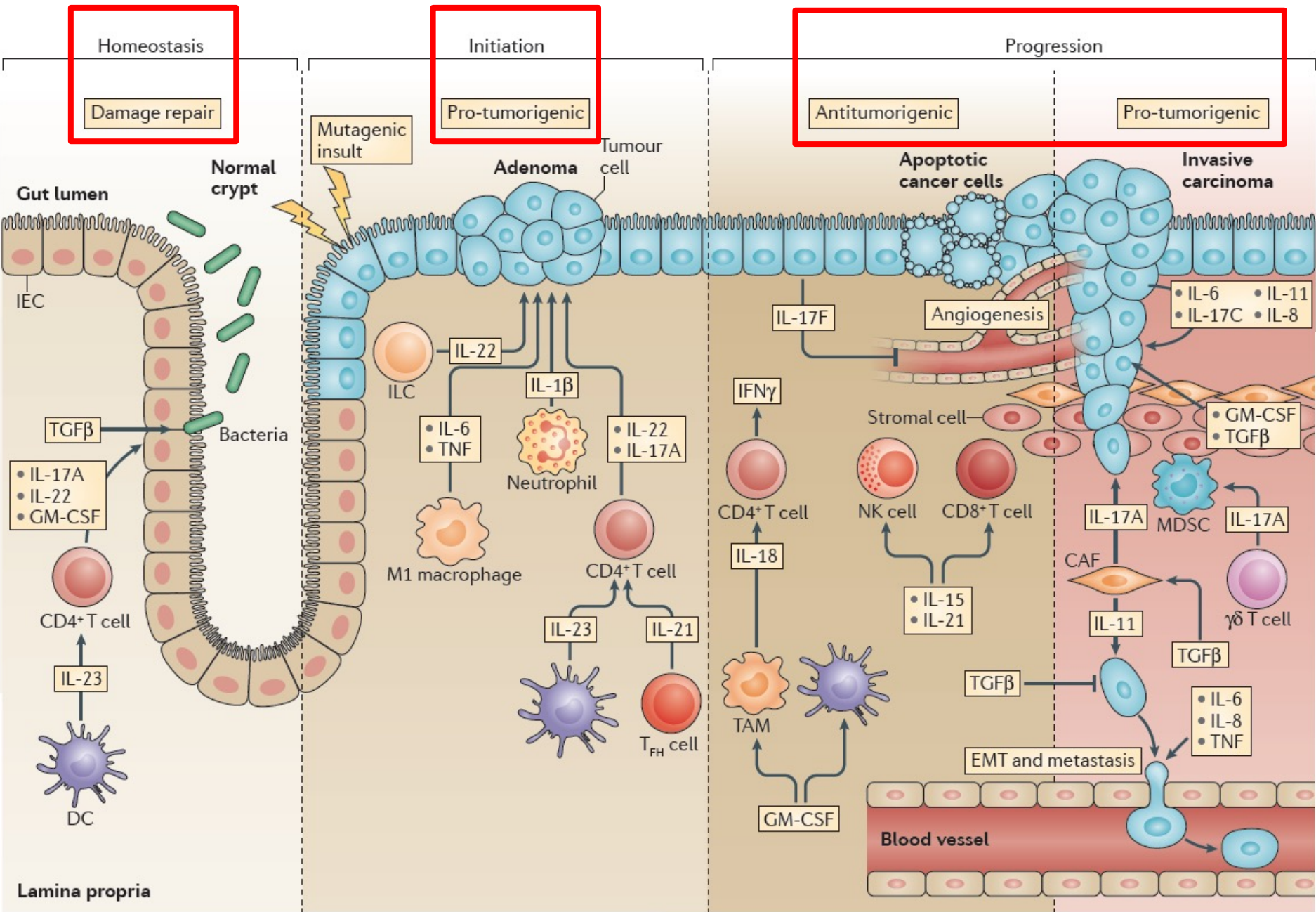
West, *Nat Rev Immunol 15:615*, 2015

Biomarkers of chronic inflammation in disease development and prevention: challenges and opportunities
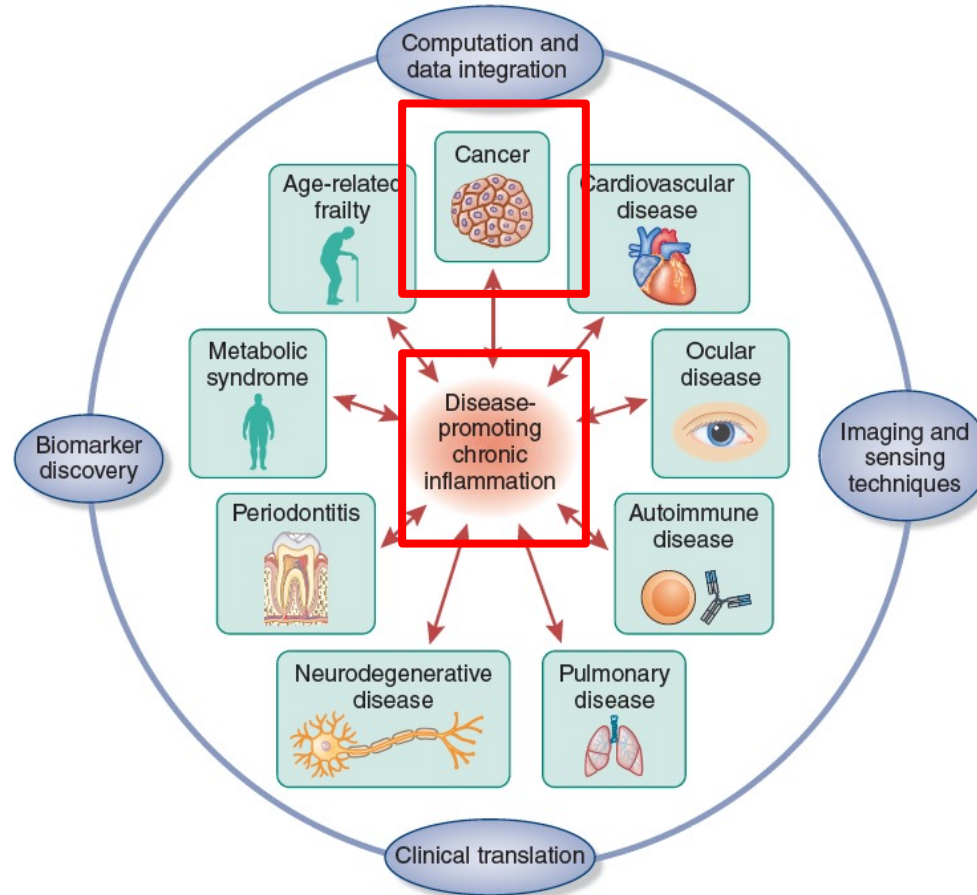
Potential contributors and therapeutic targets:
- Accumulation of senescent cells
- Unresolved infection
- Dysbiosis
- Activated microglia and macrophages
- Cytokine and chemokine dysregulation
- Imbalance between pro-inflammation mediators and pro-resolution mediators
- Gene mutations
- Epigenetic modifications
- Lifestyle risk factors

Obesity

A
resting microglia
normal HPA-axis feedback
LPS microbiota

B
TLR4↑ altered HPA-axis
brain inflammation, gliosis, cytokines
LCFA
LPS changed microbiota
body adiposity
diet

Enhanced: fever, sickness behavior, cognitive and emotional alterations, risk for diabetes, cardiovascular disease, mortality to infections?

systemic infection / inflammation (LPS)

FIGURE 3. Obesity affects responsiveness to systemic infection and inflammation

Rummel, *Physiology 31*:117, 2016

BEING OVERWEIGHT INCREASES RISK FOR 8 TYPES OF CANCER

colorectal, endometrial, esophageal, gallbladder, kidney, ovarian, pancreatic and postmenopausal breast cancer

CANCER SURVIVORS

MORE THAN **TWO-THIRDS** OF THOSE DIAGNOSED WITH CERTAIN CANCERS ARE OVERWEIGHT OR OBESE.

PHOTO © YUSAKU TAKEDA / ISTOCK / THINKSTOCK

Targeting Inflammation in Cancer Prevention and Therapy

Table 1. Risk factor and inflammatory conditions correlated with cancer development and estimated new case from Cancer Statistics, 2016

Cancer type	Estimated new cases in 2016	Risk factors correlated with inflammation
Pancreas	53,070	Cigarette smoking, chronic pancreatitis diabetes, obesity, Lynch syndrome
Lung and bronchus	224,390	Cigarette, cigar and pipe smoking, bronchitis
Stomach	26,370	*H. pylori*
Colon and rectum	134,490	Obesity, physical inactivity, long-term smoking, alcohol consumption, chronic inflammatory bowel disease (e.g., ulcerative colitis or Crohn disease)
Esophagus	16,910	Reflux esophagitis, Barrett esophagus
Lymphoma	81,080	Epstein-Barr virus, HIV
Liver and intrahepatic bile duct	39,230	HBV and/or HCV, heavy alcohol consumption, obesity, diabetes, tobacco smoking, cholangitis
Melanoma of the skin	76,380	Skin inflammation
Uterine cervix	12,990	HPV
Uterine corpus (endometrium)	60,050	Obesity and abdominal fatness Lynch syndrome and diabetes
Brest cancer	246,660	Obesity, long-term, heavy smoking, physical inactivity, and alcohol consumption
Urinary bladder	76,960	Smoking, cystitis/bladder syndrome
Oral cavity and pharynx	48,330	Excessive alcohol consumption. HPV infection, tobacco use
Kidney and renal pelvis	62,700	Obesity and tobacco smoking, chronic renal failure
Leukemia	60,140	Obesity, cigarette smoking, T-cell leukemia virus type I (HTLV-I)

Todoric, *Cancer Prev Res*, 9:895, 2016

Cancer Prevention Interventions

AVAILABLE TODAY BECAUSE OF RESEARCH

MEDICATIONS

proven to reduce risk of breast and colon cancers in those at increased risk.

LIFESTYLE CHOICES

such as avoid or quit tobacco, limit alcohol, avoid known carcinogens, keep active & avoid obesity.

TREATMENTS FOR INFECTIONS

known to increase cancer risk, including hepatitis C, HIV, and H. pylori.

SCREENING TESTS

that allow removal of precancerous lesions, such as colon polyps.

VACCINES TO PROTECT

against infection with human papillomavirus (HPV) and hepatitis B.

SURGERY

to remove tissues at risk , such as for women with increased risk of breast and ovarian cancer.

prevention.cancer.gov
NCI Division of Cancer Prevention

Philip Castle, Ph.D., M.P.H., joined NCI in July 2020 as **director of the Division of Cancer Prevention (DCP)**. To mark his first year as DCP director, Dr. Castle discusses DCP's priority areas and his vision for making more rapid progress in cancer prevention.

- **What do you see as the most promising possibilities for, and barriers to, real progress in cancer prevention over the next decade?**

- There are a variety of areas of promise. One area that we're working very hard to develop is **precision cancer prevention**. What I mean by that is using what we know about a person—their genetics, risk factors, lifestyle—to tailor our prevention strategies. And as an anchor to that, we're using molecular sciences to flesh out the best approaches for advancing this work.

- At the same time, we want to democratize cancer prevention, developing new strategies that make proven prevention measures more broadly accessible, particularly for underserved populations. For instance, efforts to expand the use of self-sampling with HPV DNA testing for cervical cancer screening.

- As for barriers to progress, I see two major issues. One that has been called the **"prevention paradox":** If we're successful with prevention, there's nothing to observe because we've avoided a bad outcome—cancer. It's what I call an "event bias," where we tend to notice the events that occur rather than the absence of events.

- A second barrier is the **benefits-to-harms ratio** of any prevention-focused interventions. When you're talking about cancer prevention, you're primarily dealing with generally healthy people. So the tolerance for any side effects from a prevention [intervention](#) is very low. Many people won't get cancer in their lifetime, and you don't want to harm anybody who was never going to get cancer.

"Interception" Research

✓**Prevention**
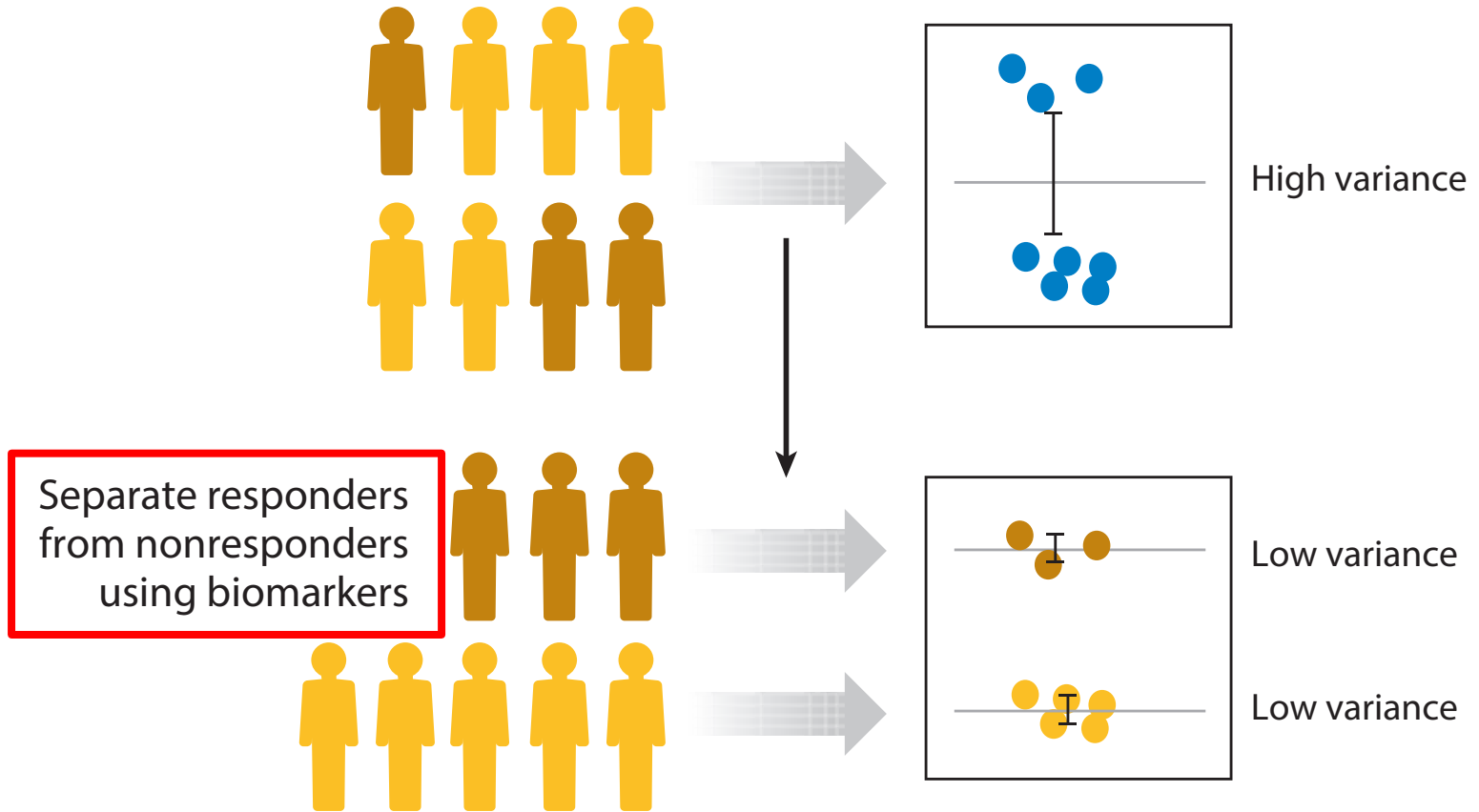✓**Early Detection**
✓**Early Intervention**

- **Prevention is a broad topic. Have you identified priority areas for the division?**

- One is developing preventive agents. That involves **identifying "druggable" targets** for preventive drugs and developing the drugs themselves. That work is anchored in molecular sciences, understanding cancer-promoting signaling pathways in cells and how to interrupt them, and using that information to develop new pharmacologic agents or repurpose existing drugs for use in cancer prevention.

- The second research arc is **discovering <u>biomarkers</u>** that can identify who is at increased risk of cancer. Eventually, those two areas will come together: We will be able to use a biomarker that can identify who's at risk, and then provide a preventive agent to mitigate that risk, based on an individual's underlying biology.

- Once we understand the biology and genetics of cancer-related and treatment-related symptoms—that is, **symptom science**—we can better tailor the use of current medications to prevent and/or alleviate symptoms and develop new, more effective medications in the future.

- This has an important impact on **<u>survivorship:</u>** The longer we keep people with cancer healthy, the more likely they are going to be able to get the next-in-line therapy and even therapies that have not been invented today but will be tomorrow.

Cancer chemoprevention by dietary constituents: a tale of failure and promise

Andreas J Gescher, Ricky A Sharma and William P Steward

✓**Heterogeneity in response**
✓**Dietary bioactives and drugs are pleiotropic**
✓**Need to elucidate molecular mechanisms of action**

What Contributes to Individual Variability?

Separate responders from nonresponders using biomarkers

High variance

Low variance

Low variance

Does One Approach Fit All?

MORTALITY

Normal BMI Metabolically healthy	Obese BMI Metabolically healthy	Normal BMI Metabolically unhealthy	Obese BMI Metabolically unhealthy
26%	10%	8%	21%
• Reduced fat	• Excess subcutaneous > visceral fat	• Chronic illness	• Excess visceral > subcutaneous fat
• Increased muscle	• Increased muscle	• Muscle loss (sarcopenia)	• Muscle loss (sarcopenia)
• Increased fitness	• Increased fitness	• Excess visceral fat	• Reduced fitness
• Normal insulin sensitivity	• Hyperinsulinemia	• Reduced fitness	• Hyperinsulinemia
• Normal blood sugar	• Normal insulin sensitivity	• Insulin resistance	• Diabetes
• Low cardiovascular risk	• Normal blood sugar	• Diabetes	• Dyslipidemia
	• Mild cardiovascular risk	• Inflammation	• Inflammation
		• High cardiovascular risk	• High cardiovascular risk
		• High cancer risk	• High cancer risk

Ahima, *Science* 341:856, 2013

What Contributes to Heterogeneity in Response?

Gut Microbiome

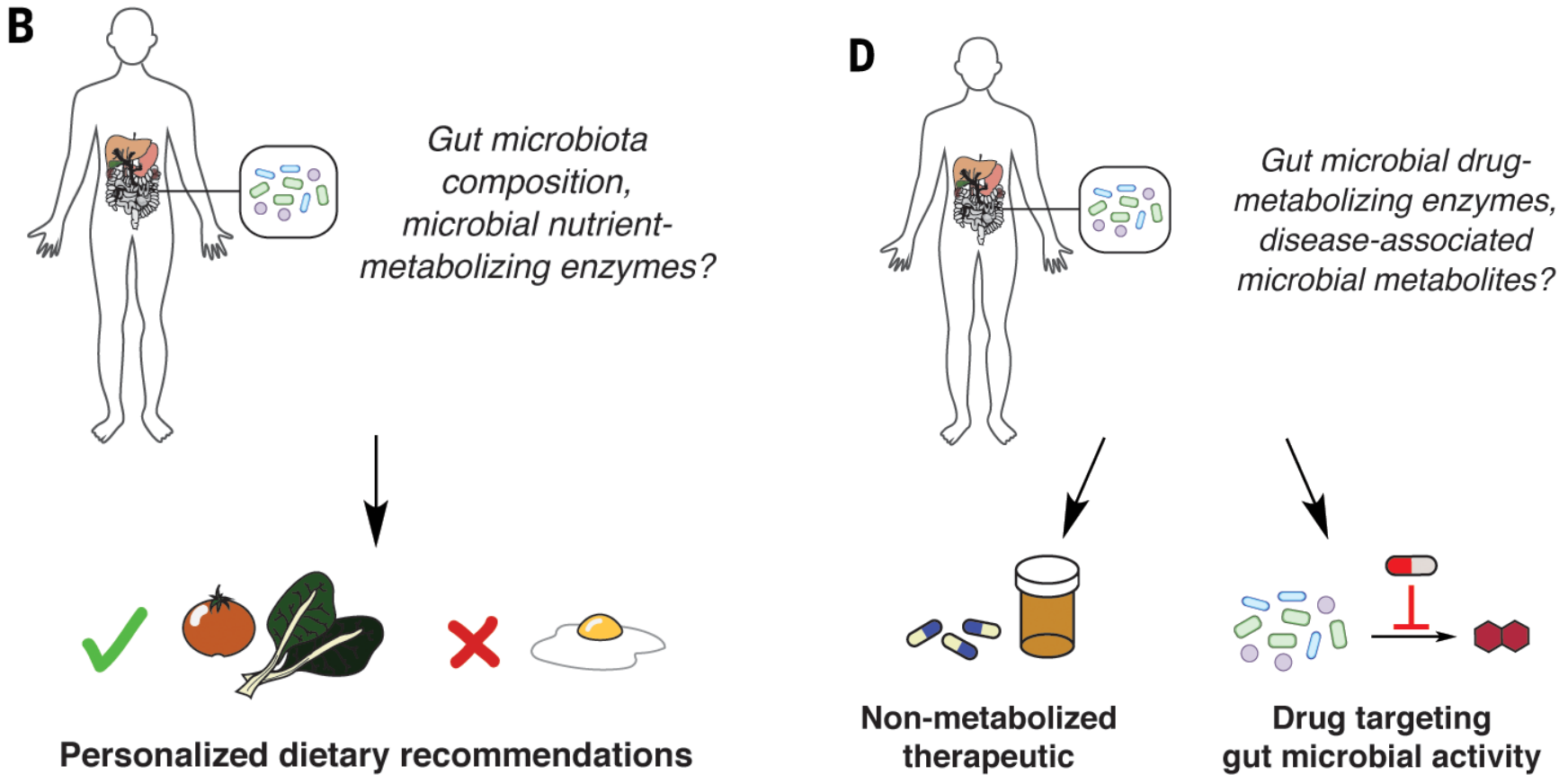### Gut microbiota is associated with many chronic diseases in humans

Brain
- Autism spectrum disorder
- Stress
- Stroke

Lung
- Allergic asthma

Liver
- NAFLD/NASH

Skin
- Atopic dermatitis

Adipose tissue
- Inflammation
- Obesity

Whole body
- Type 2 diabetes
- Systemic lupus erythematosus
- Undernourishment
- Atherosclerosis

Food genome

Schroeder, *Nature Medicine* 22:1079, 2016
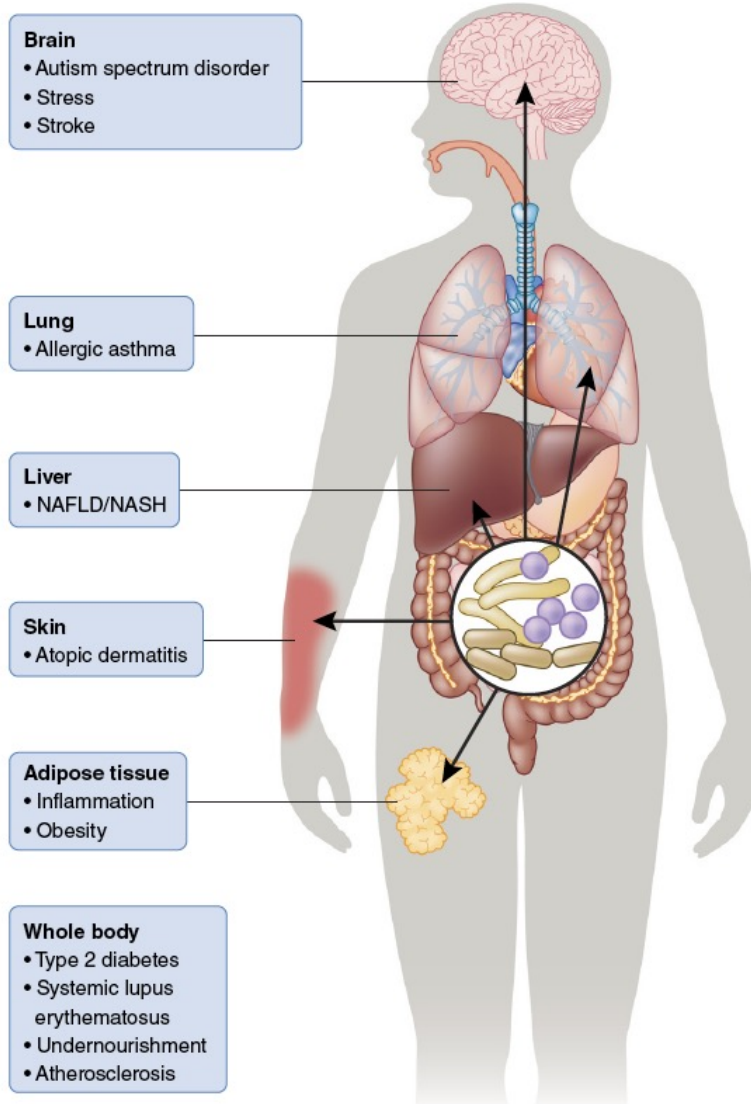
Host-Microbe Interactions
Drug/Diet Responsiveness & Failures

Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity
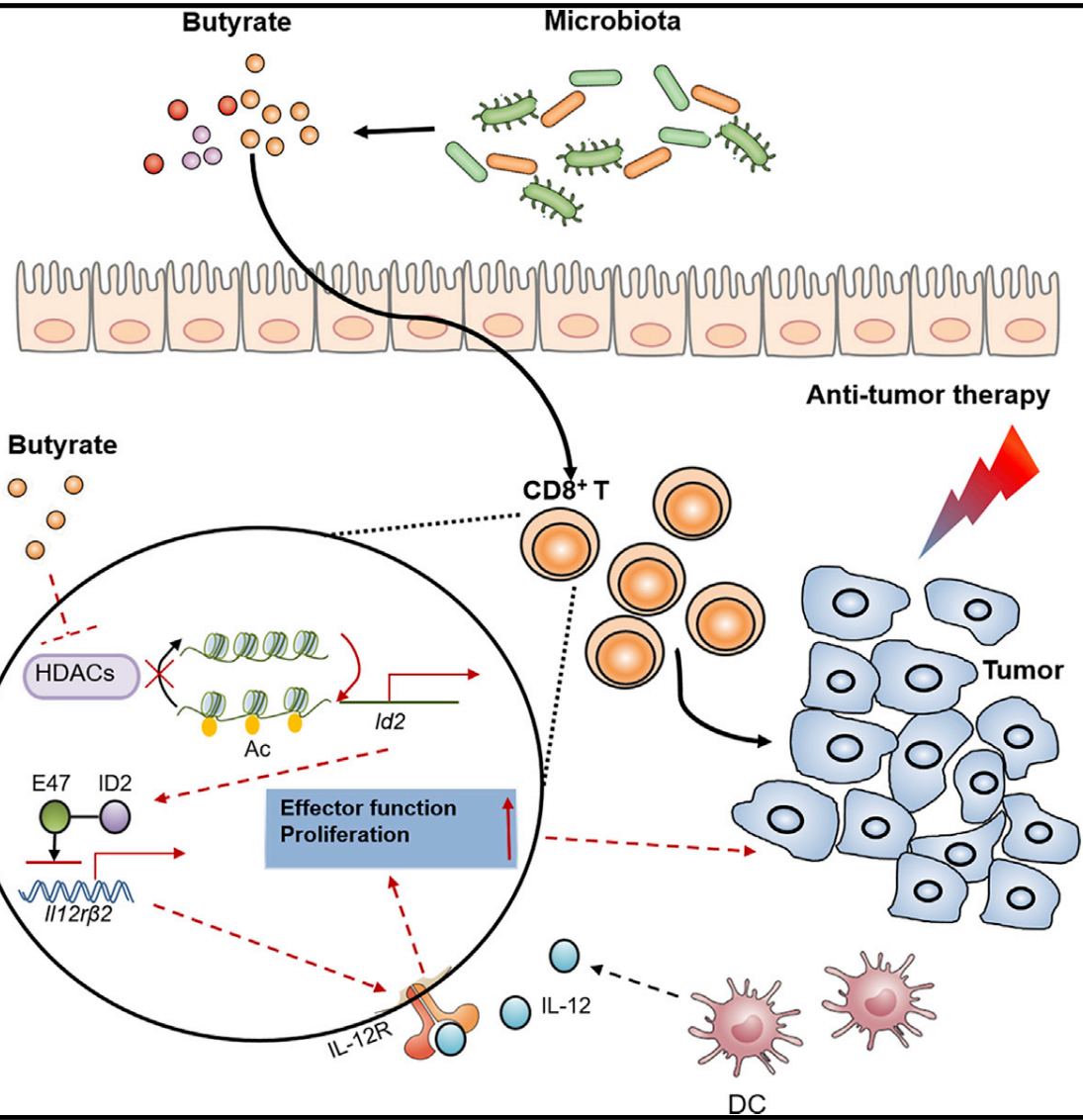
- Gut microbial metabolites improve chemotherapy efficacy via regulating CD8+ T cells

- Butyrate supplementation improves the antitumor therapy efficacy

He, *Cell Metabolism 33:988*, 2021

What Contributes to Heterogeneity in Response to Treatment?

Cell Heterogeneity

Table 2 | **Transcriptional identified consensus molecular subtypes (CMS)**

Tumour subtype	CMS1 MSI/immune	CMS2 canonical	CMS3 metabolic	CMS4 mesenchymal
Proportion*	~15%	~40%	~10%	~25%
Genomic features	Hypermutated	SCNA high	Mixed MSI	SCNA high
Genetic drivers	*BRAF*	*APC*	*KRAS*	Unknown
Associated precursors	Serrated	Tubular	Unknown	Serrated
Gene-expression signature	Immune	Wnt/MYC activity	Metabolic deregulation	• TGFβ / EMT • High stromal content
Prognosis	Intermediate	Good	Intermediate	Poor

EMT, epithelial–mesenchymal transition; MSI, microsatellite instability; SCNA, somatic copy-number alterations.*Approximately 10% of cases are not reliably classified into one tumour subtype. Adapted with permission from Guinney J. *et al.* The consensus molecular subtypes of colorectal cancer. *Nat. Med.* **21**, 1350–1356 (2015).
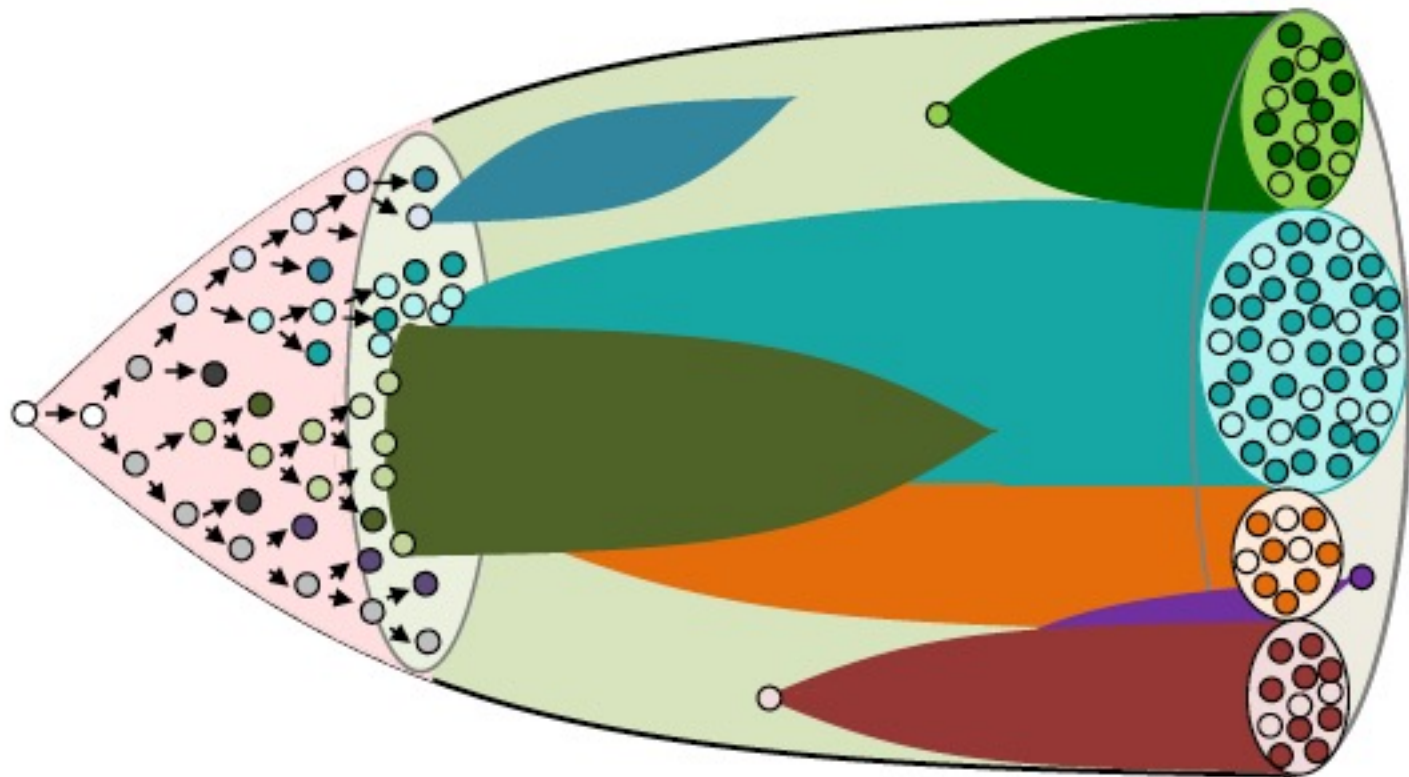
LETTER

Tumour cell heterogeneity maintained by cooperating subclones in Wnt–driven mammary cancers

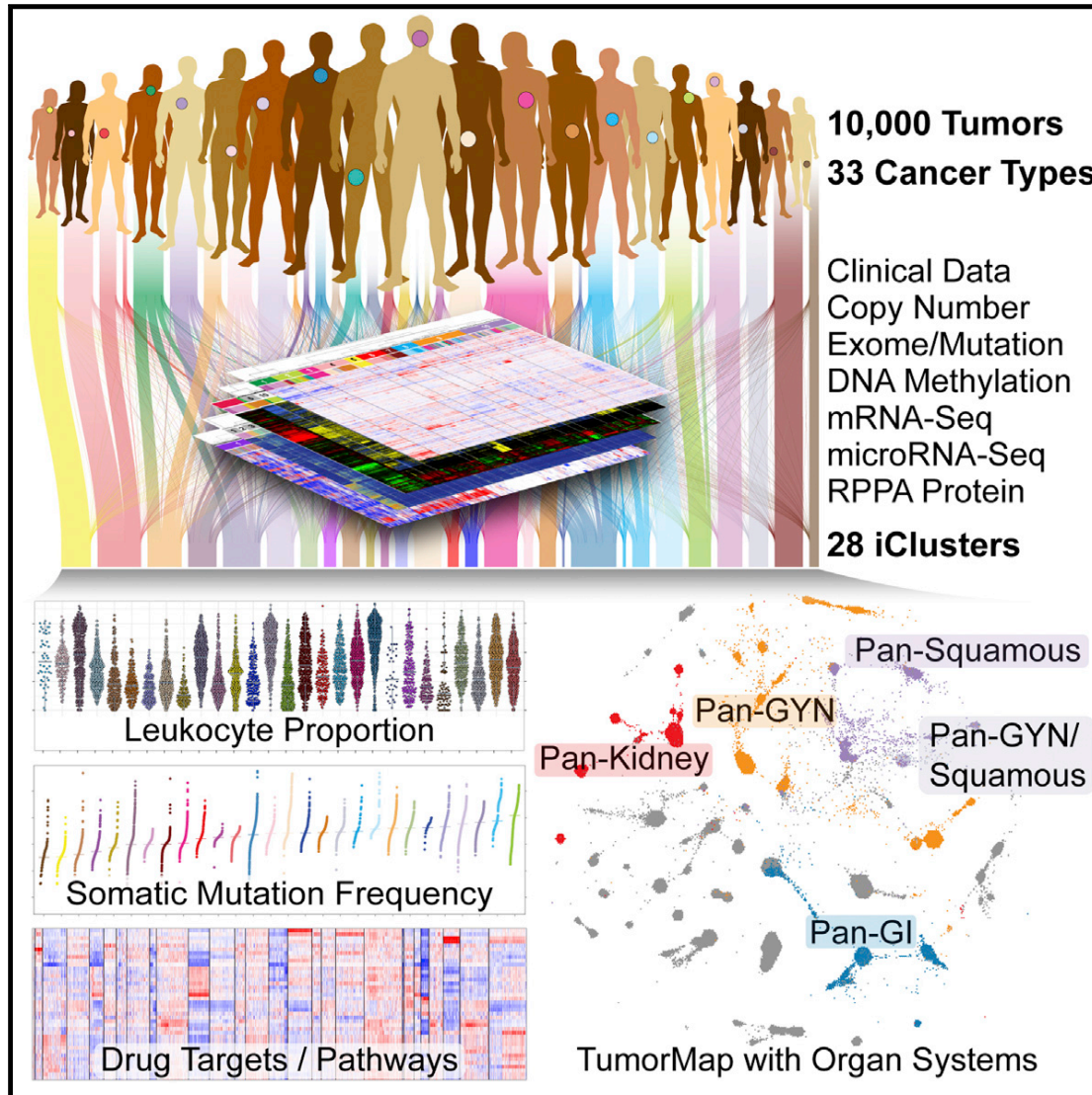Allison S. Cleary[1,2], Travis L. Leonard[1,2], Shelley A. Gestl[1,2] & Edward J. Gunther[1,2,3]

Modeling the process of human tumorigenesis

Depiction of subclonal evolution and diversification of cell types in developing malignant populations

Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer

Comprehensive, integrated molecular analysis identifies molecular relationships across a large diverse set of human cancers, suggesting future directions for exploring clinical actionability in cancer treatment.
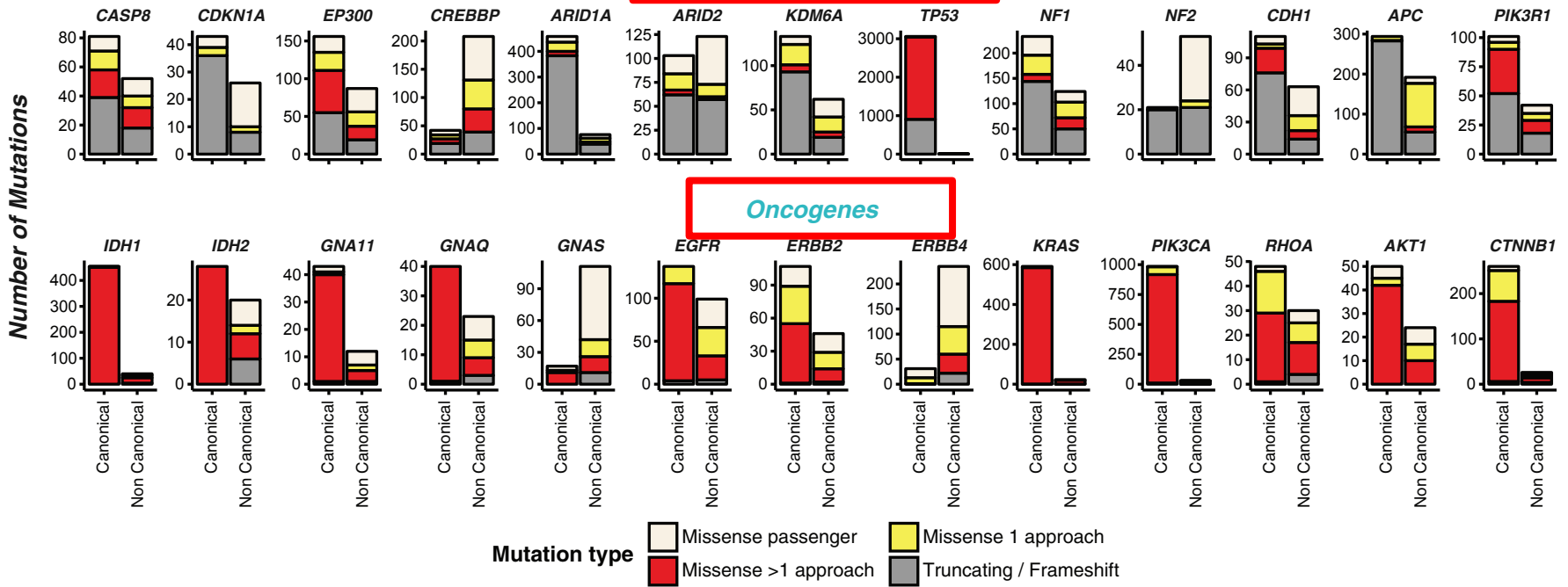
Hoadley, *Cell 173*:291, 2018

The Immune Landscape of Cancer
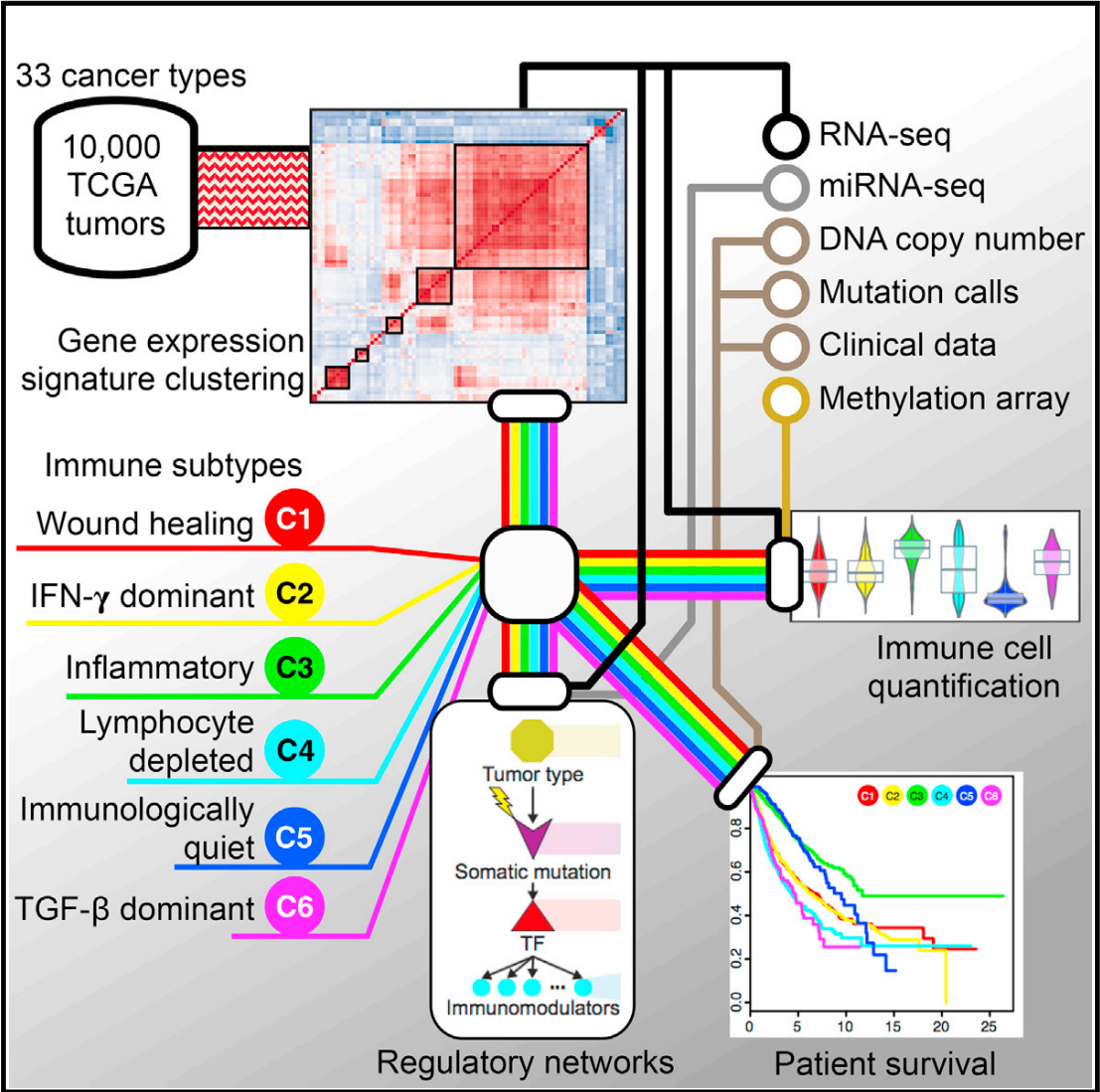
Comprehensive Characterization of Cancer Driver Genes and Mutations


Bailey, *Cell 48*:371, 2018

Unravelling biology and shifting paradigms in cancer with single-cell sequencing

Table 1 | **Overview of the most commonly used single-cell sequencing technologies**

	Single-cell genomics		**Single-cell transcriptomics**	
Chemistry	DOP-PCR[24,31,86]	MDA[30,164,192]	Full-length cDNA[27,98]	Transcriptome tagging[28,29]
Advantages*	Uniformity of coverage	High genome coverage	Coverage across entire transcript	mRNA molecule tagging and counting; amenable to high multiplexing
Disadvantages*	Low genome coverage	Non-uniform amplification of genome	Not yet compatible with highly parallel multiplexing	Does not provide coverage of entire transcript
Application	CNA analysis	SNV analysis	In-depth analysis of single-cell transcriptome	Highly quantitative analysis of transcript abundance across many cells

CNA, copy number alteration; DOP-PCR, degenerate oligonucleotide priming-PCR; MDA, multi-displacement amplification; SNV, single nucleotide variant. *Advantages and disadvantages of the methods are based on empirical, comparative studies between whole-genome amplification (WGA) and whole-transcriptome amplification (WTA) methods carried out by multiple independent groups[208–213].
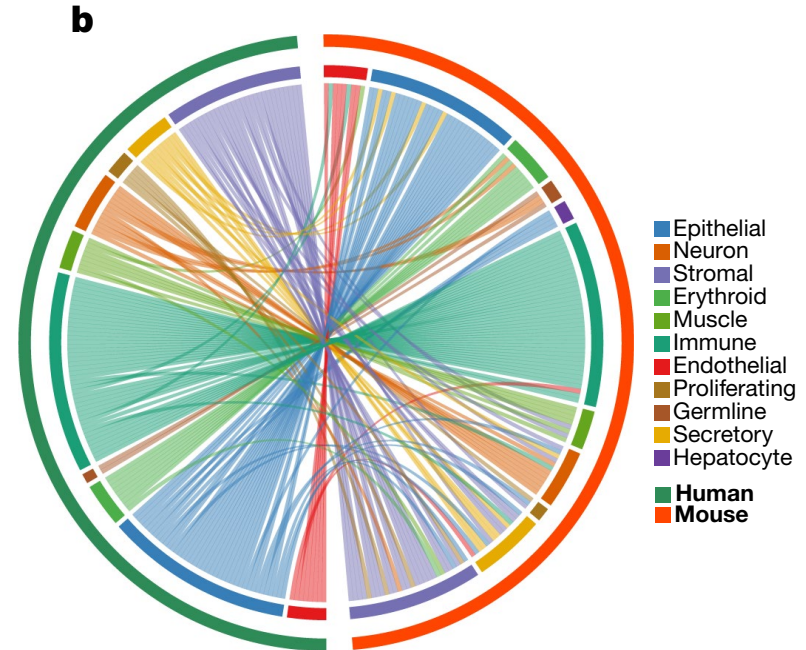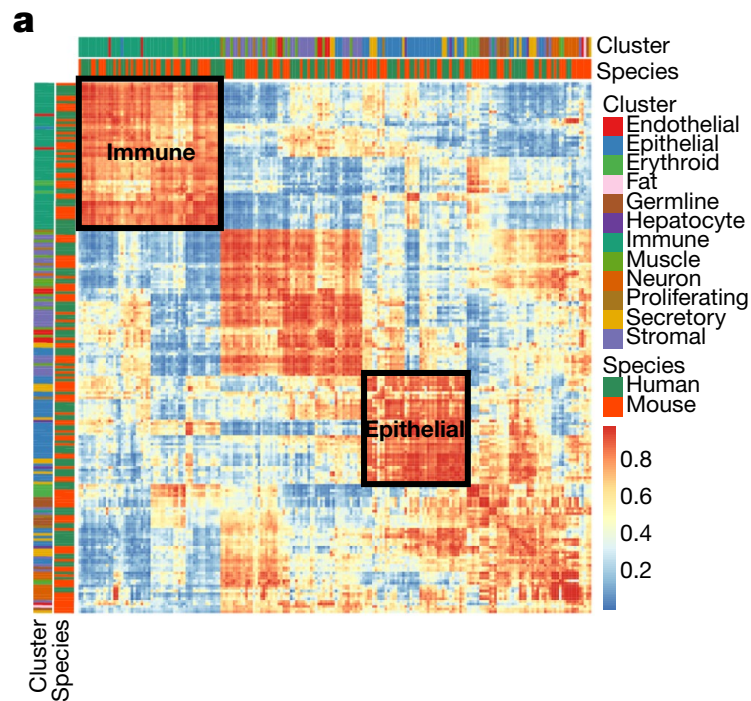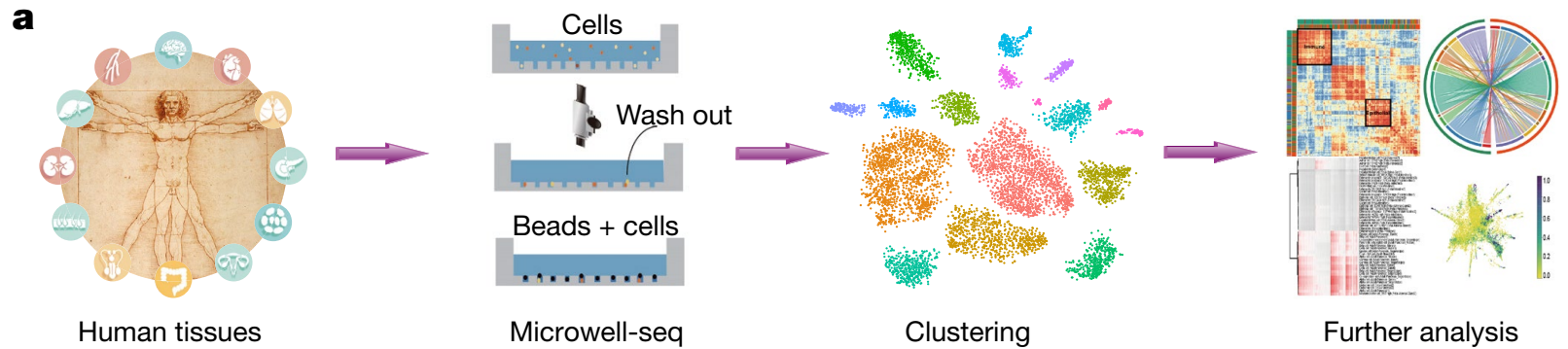
Single Cell Multi-omics
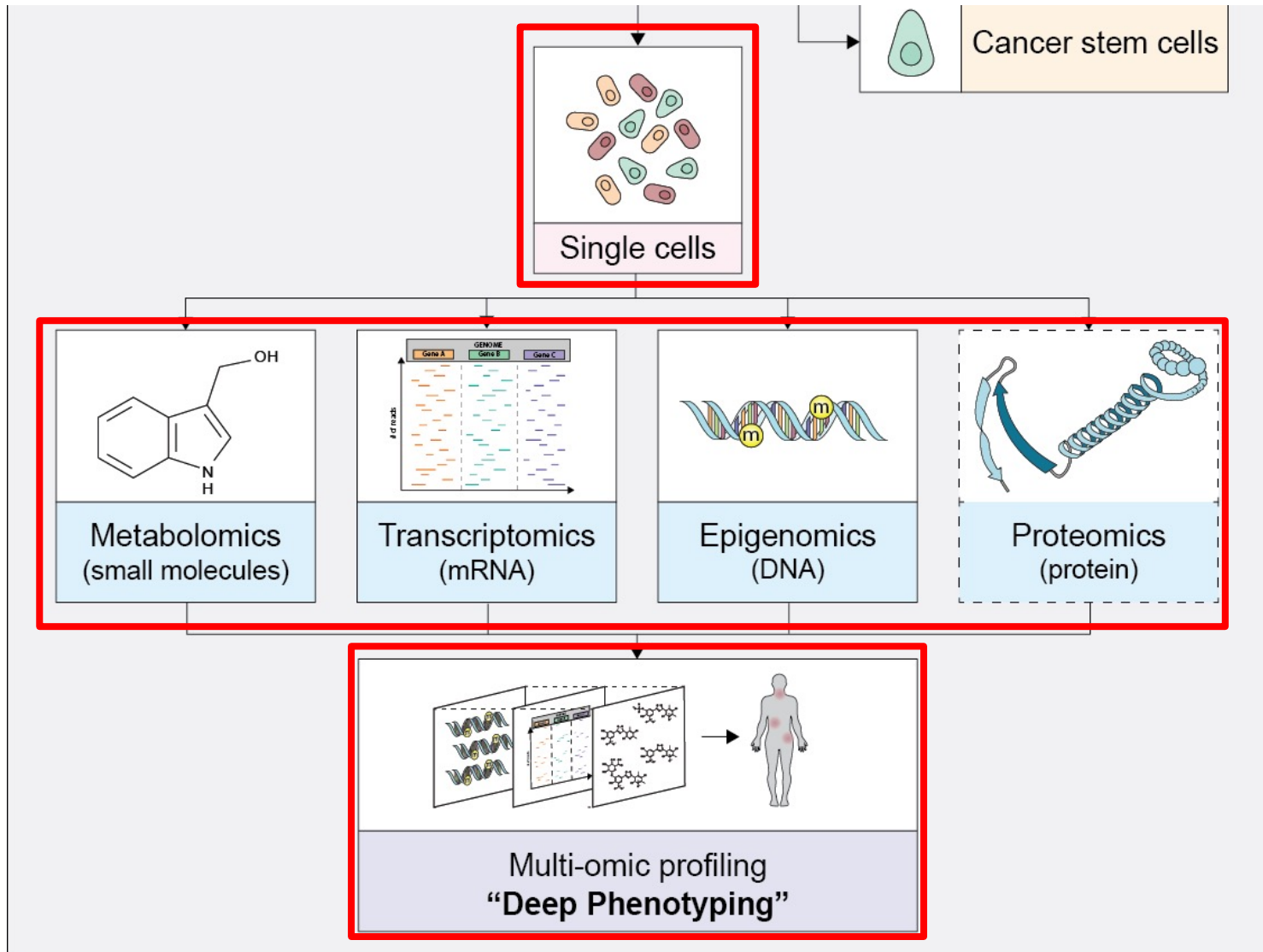
Single-Cell Metabolomics: Analytical and Biological Perspectives
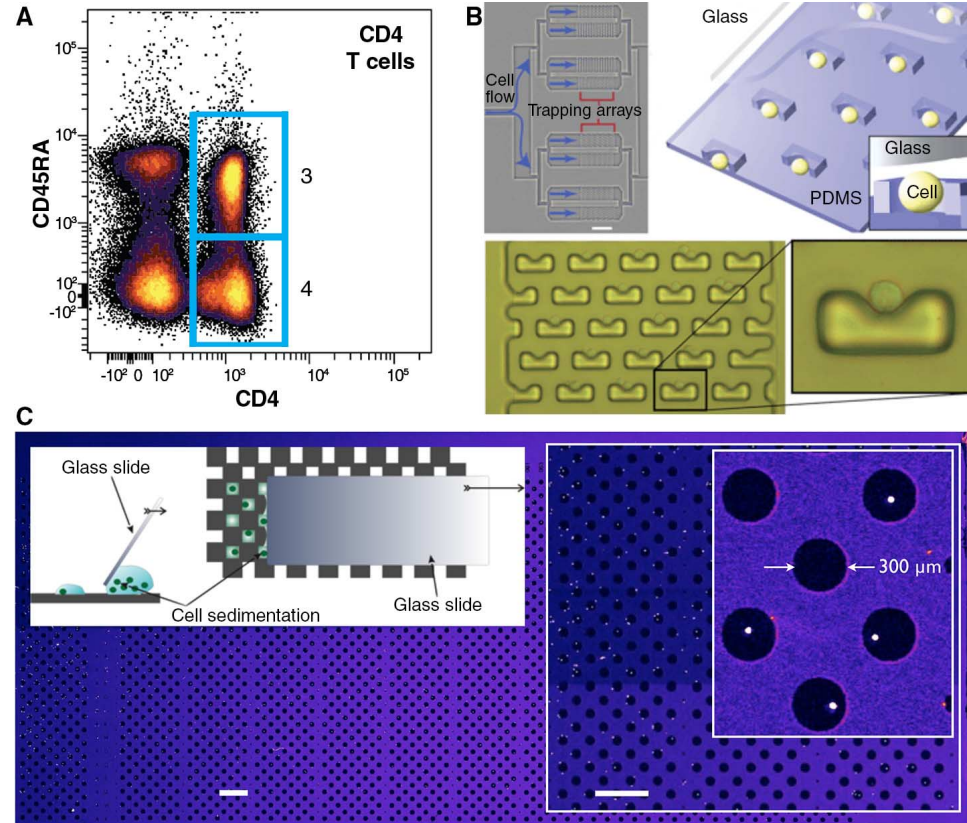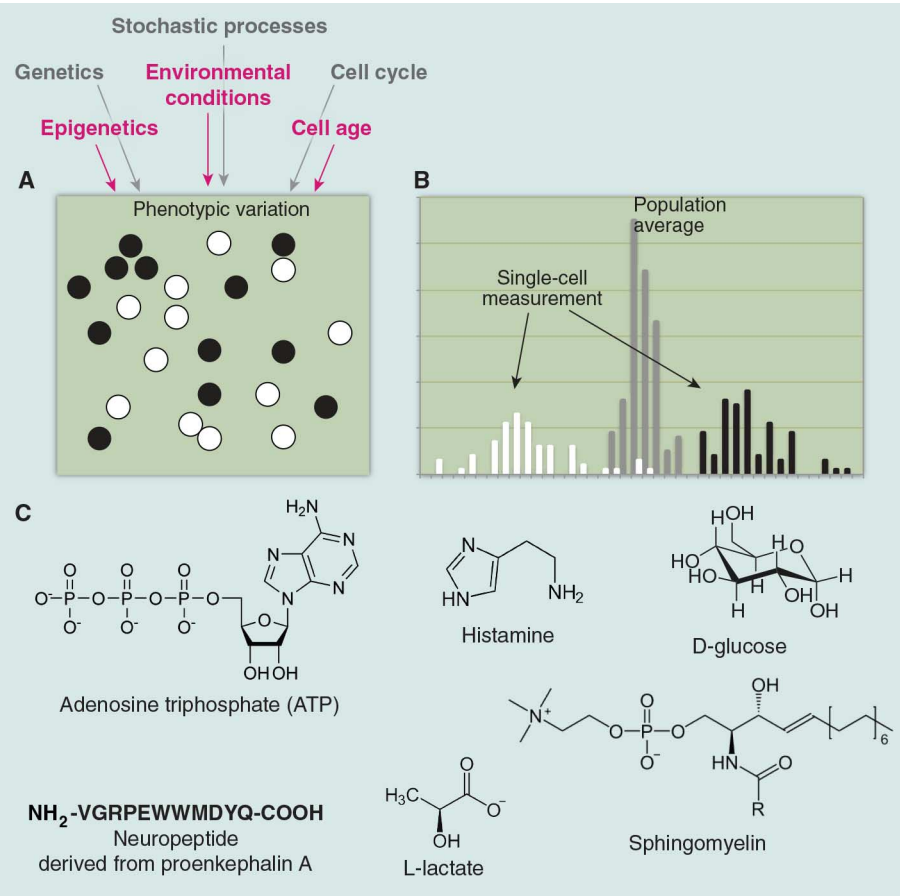
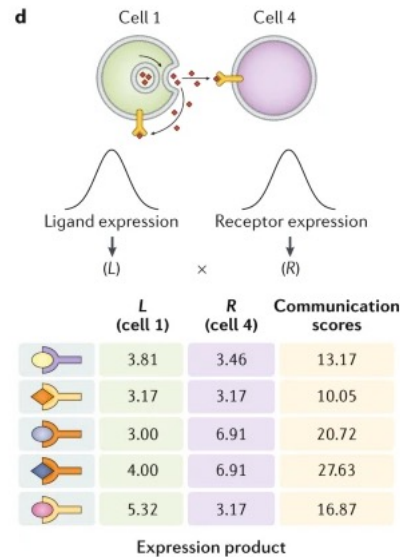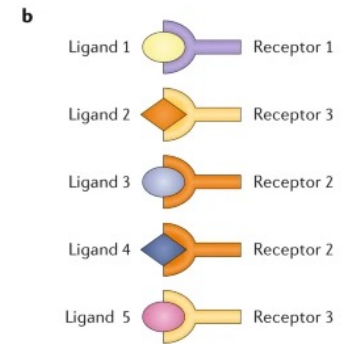# Construction of a human cell landscape at single-cell level

Cell-Cell Interactions

Single cell RNA based cellular interaction analysis:
Based on the expression level of ligand and receptor pairs

Types of interactions between cells:
1. Autocrine
2. Paracrine
3. Juxtacrine
4. Endocrine
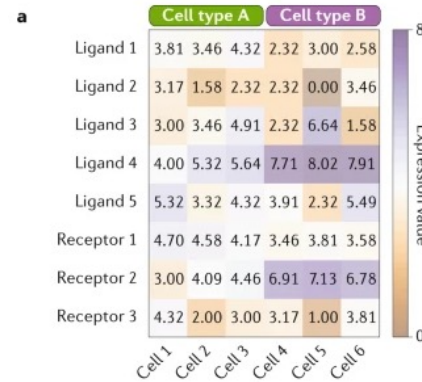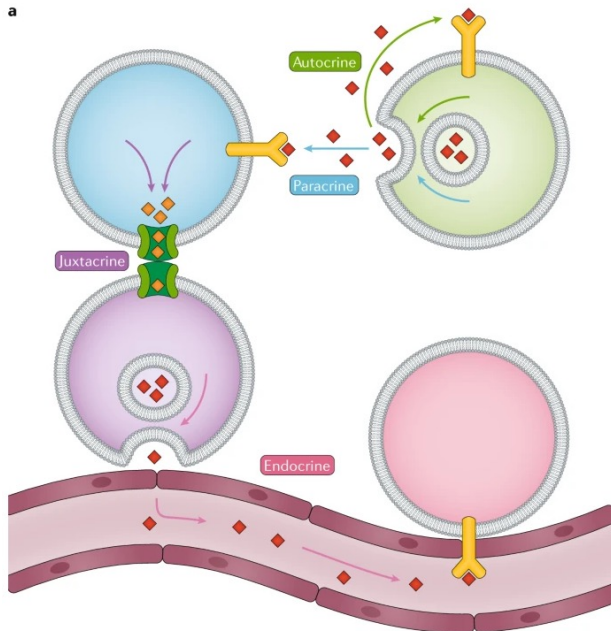
Product of ligand and receptor expression as the score of the corresponding L-R pair

Inferred interaction numbers (L-R pairs)

WT

KO
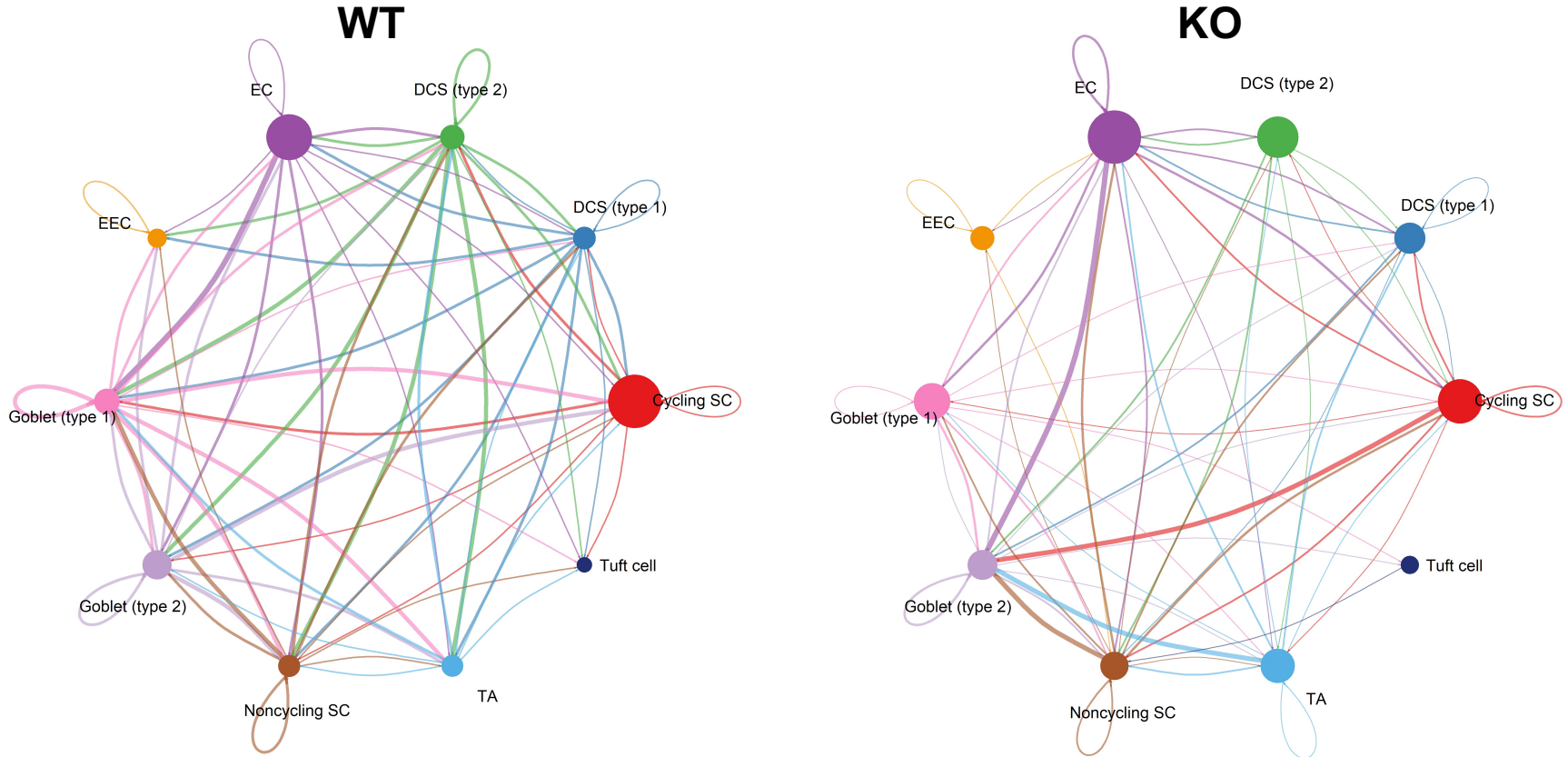
Vertex size: number of cells
Edge thickness: number of inferred L-R interactions
Color of edges: consistent with sender cells

Deep Phenotyping

Humanized mouse models

Cancer cell robustness   Tumor stem cells   Drug targets   Metastasis   Therapy

Human tumor

Transplant into SCID mice
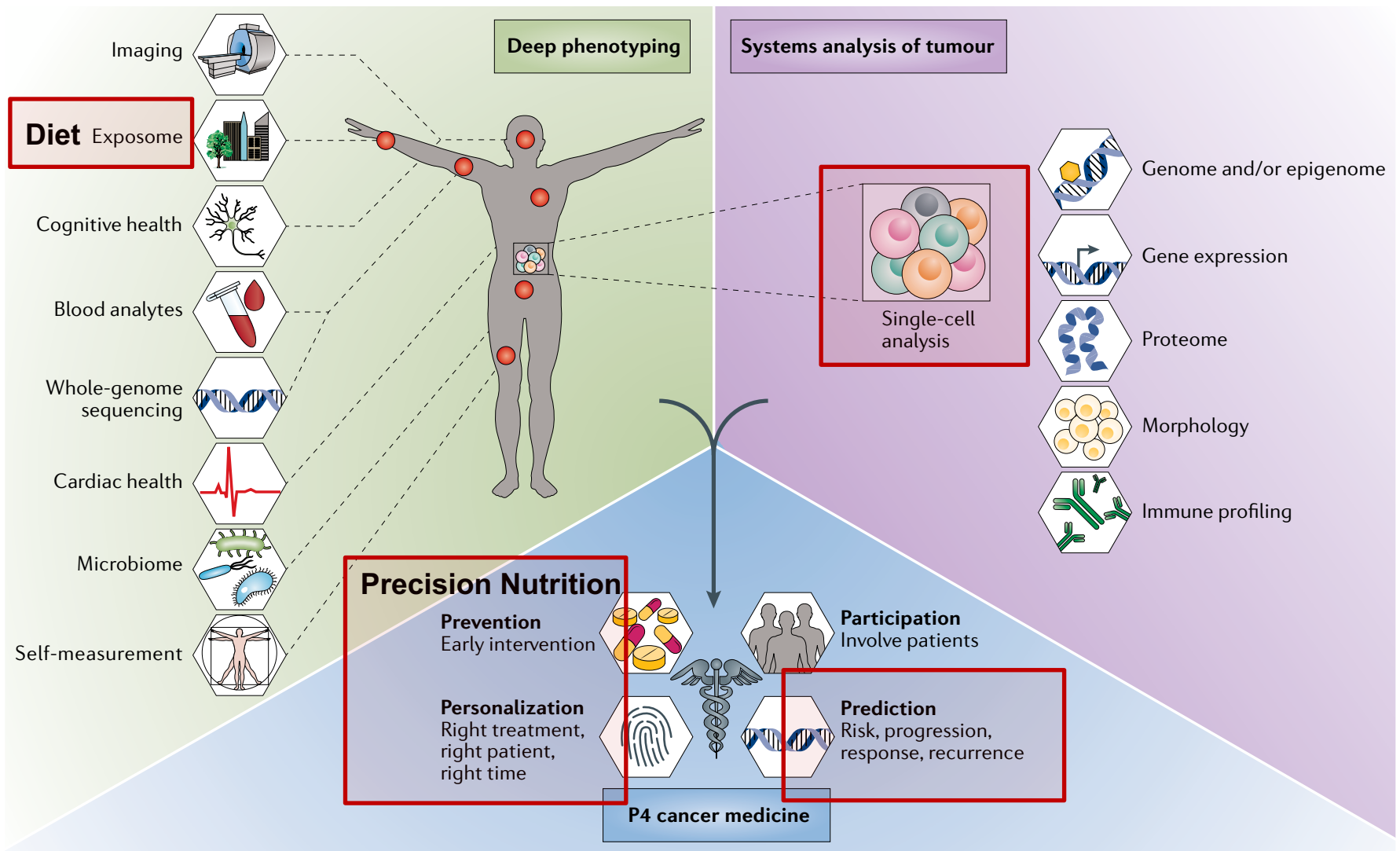
Guide clinical approaches
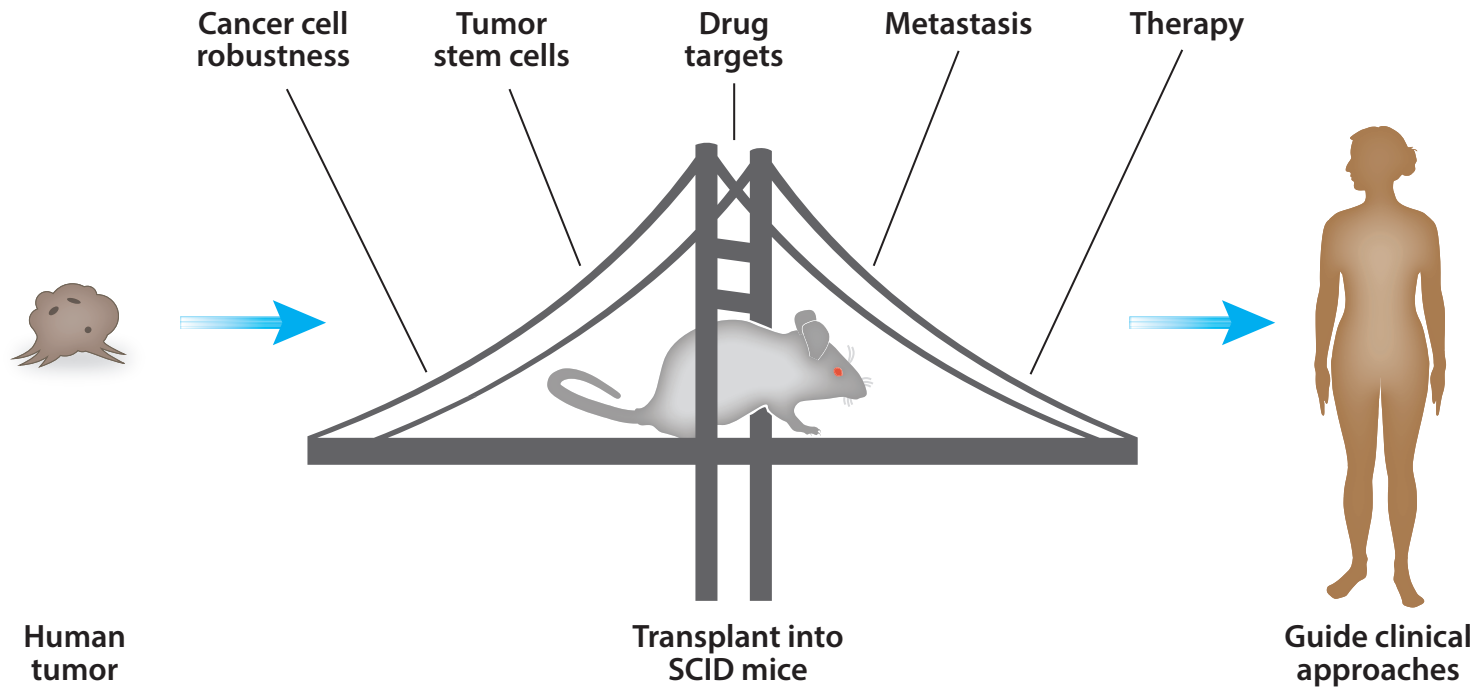
Patient-derived orthotopic xenografts: better mimic of metastasis than subcutaneous xenografts

Hoffman, *Nature Rev Cancer 15:*451, 2015; Salahudeen, *Nature Medicine 21:*215, 2015

...ids

...anizing 3D ...ormal gut

Basic research

External stimuli
Cell–cell interaction

Developmental processes

PSCs

AdSCs

Healthy

Biobanking

PSCs

AdSCs

Differentiation

Growth factors

Organoid culture in ECM

Biobank

Patient

Cell therapy   Drug development

Genetic engineering

Precision medicine

Pathogen analyses   Genomic analyses   Screening for disease-related genetic variants   Metabolomic analyses

Disease modelling

8

13

Kim, *Nat Rev Mol Cell Biol* **21:571, 2020**

Sato, *Nature* **459:262, 2009**

"Interception" Research

✓**Prevention**
✓**Early Detection**
✓**Early Intervention**

- **A big part of prevention is early detection. There's been recent progress in the development of multi-cancer early detection tests. What are your thoughts about these tests?**

- The big question is: Can we detect the cancer at an early enough stage that we reduce the risk of death from that cancer? That's the litmus test for any cancer screening test.

LIQUID BIOPSY

A new, noninvasive technique that can detect disease biomarkers in:

BLOOD   URINE   SPUTUM
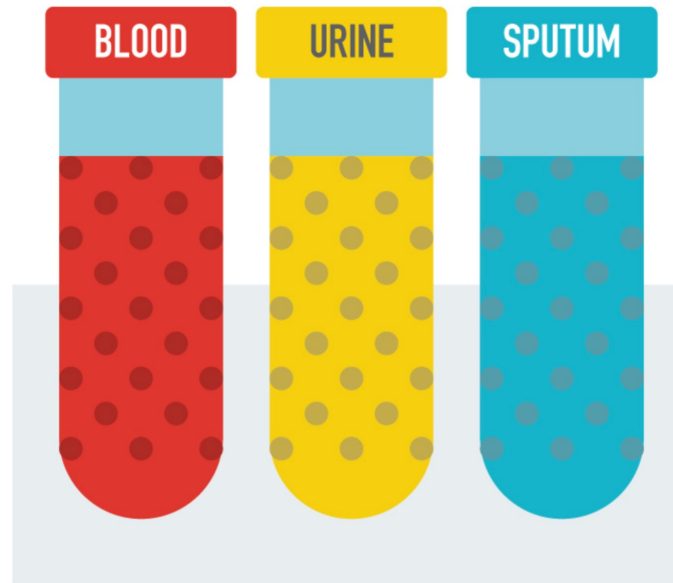
LIQUID BIOPSY IS USEFUL WHEN:

- not enough tissue sample is available
- not enough tumor tissue is in a sample
- a tumor is hard to reach
- regular monitoring is needed

LIQUID BIOPSIES ARE ANALYZED FOR:

- presence of cancer cells
- DNA
- other substances released by tumors

"Interception" Research

- ✓ **Prevention**
- ✓ **Early Detection**
- ✓ **Early Intervention**

Integrating <u>Longitudinal</u> Deep Phenotyping

Systems approach with deep phenotyping

First detection

Intervention

Return to wellness

Detectable change in measured blood analytes

Wellness

Onset of disease

Clinical disease marker

Identifying disease transition

Typical disease progression

Targeted therapy

Detectable change in clinical marker

Perturbation owing to disease

Classical precision cancer medicine

Disease progression

Clinical diagnosis

Yurkovich, *Nat Rev Clin Oncol* **17:183, 2020**

The computable cell: In silico modeling

From computable cells to personalized health

Modeling the responses of an individual's cells will enable the development of personalized treatment plans.

Patient

Cells from various tissues

Computer modeling

Personalized health plan
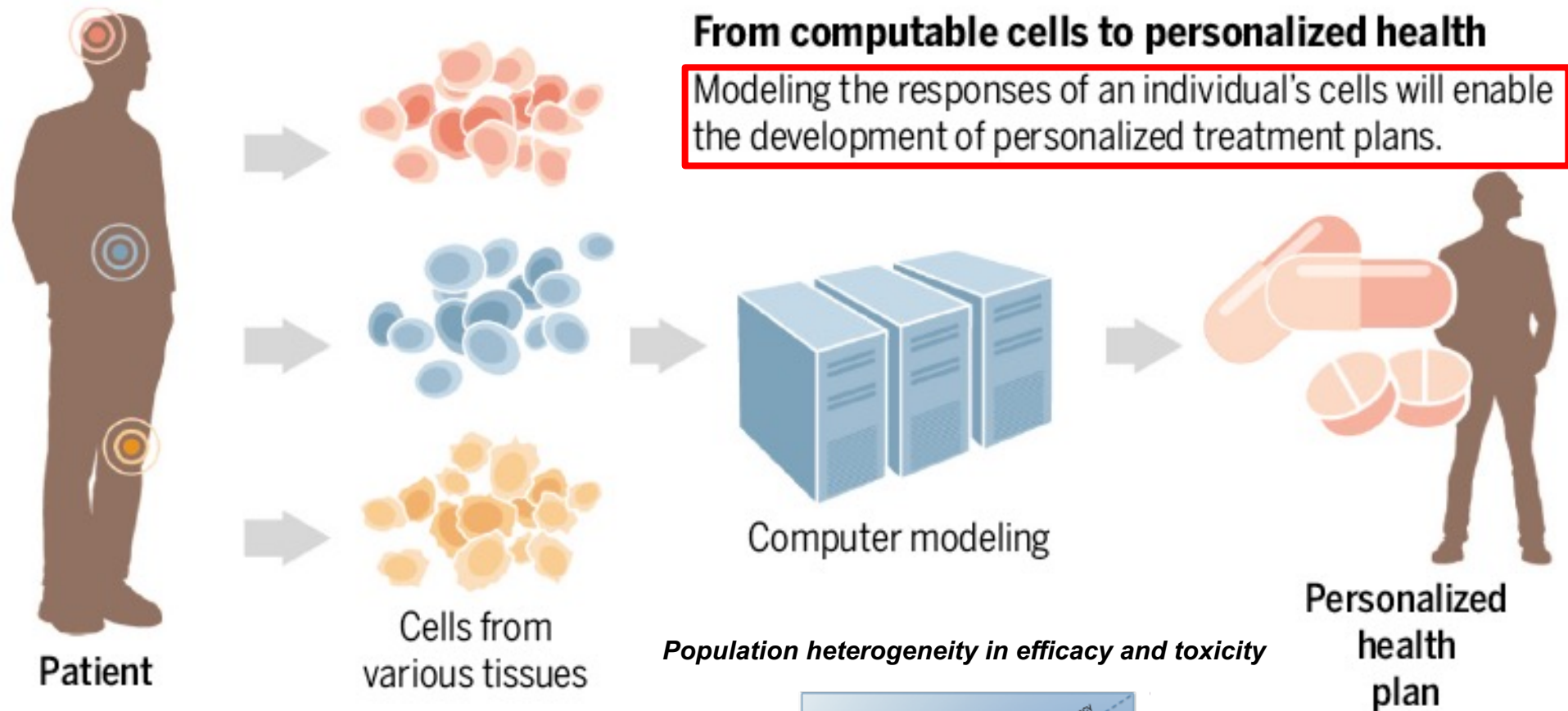
Population heterogeneity in efficacy and toxicity

Gough, *Science Signaling* **8**:408, 2015
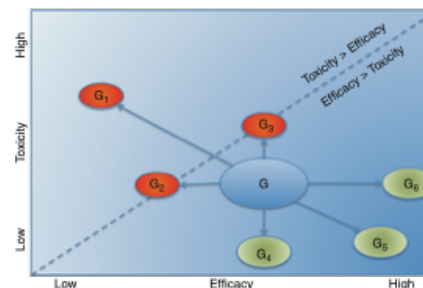
Explore Individual Variability

Armamentarium to predict biological and behavioral response patterns

Diet assessment (e.g, biomarkers for assessment of diet)

Genetic variation (e.g., studies that collect genetic data; <u>ancestral heritage</u>)

Epigenetic variation (e.g., assessment of epigenetic changes that alter metabolism and chronic disease)

Microbiome variation (e.g., effects of diet on microbiota populations and function)

Exposure variation (e.g., methods to assess environmental exposures)

Lifestyle variation (e.g., better biomarkers, instruments to assess lifestyle & behavior patterns)

Systems biology (e.g., utilize tools to assess interactions between "omic" data sets, e.g., to <u>predict outcomes</u>)

Translation to practice and policy (e.g., develop training programs in precision nutrition-guided interventions; conduct advanced evidence synthesis and dietary guidance on nutrients, foods and dietary patterns)

Systems Biology
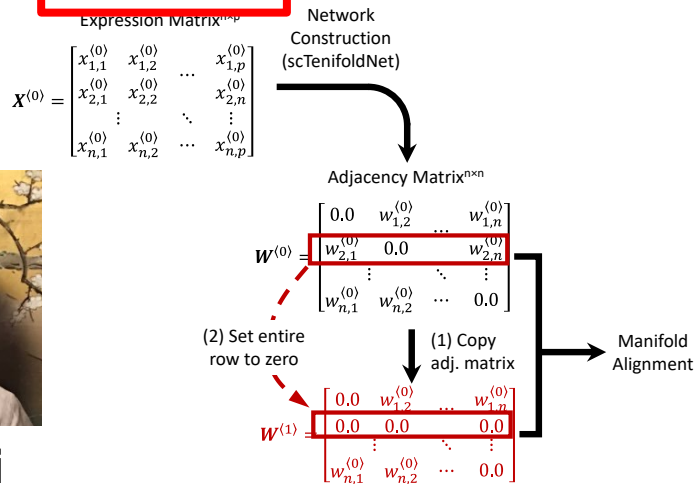# Use of a virtual machine learning KO tool (scTenifoldKn) to **predict** transcriptional changes related to stem cell reprogramming
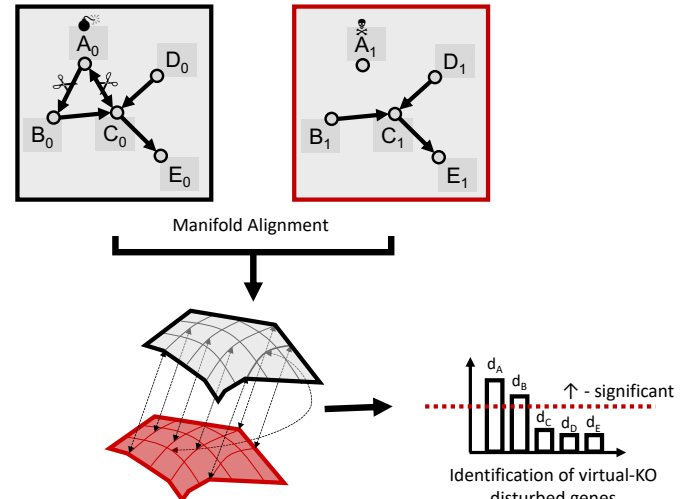

scRNAseq data

A – Network Construction
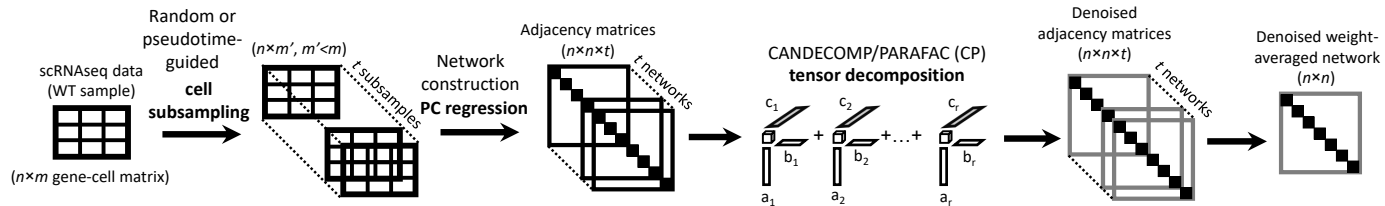
B – Virtual KO

C – Manifold Alignment

James Cai

PREVENT Cancer Preclinical Drug Development Program (PREVENT) supports the best ideas in cancer prevention using NCI contract resources

The 114 projects in PREVENT involve

68 chemo-prevention

38 immuno-prevention

8 biomarkers
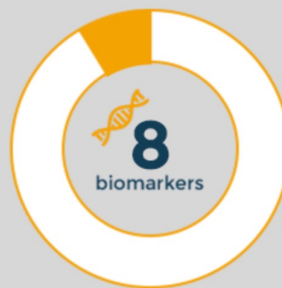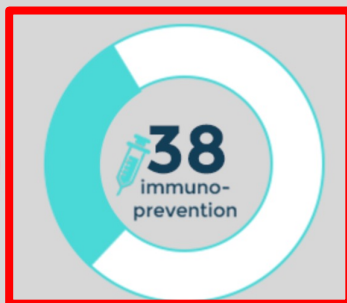
Preclinical Drug Development Pipeline

Discovery

1 Proof of Concept
Synthesis, Formulation, Immunity, Efficacy, Biomarkers

2 Secondary Testing
Efficacy Reproducibility, Regimen Optimization

3 Advanced Preclinical Development
CGMP, IND-directed GLP Toxicology, Regulatory Support

Clinical Trial

114 Projects Involve

68 Chemoprevention

38 Immunoprevention

8 Biomarkers
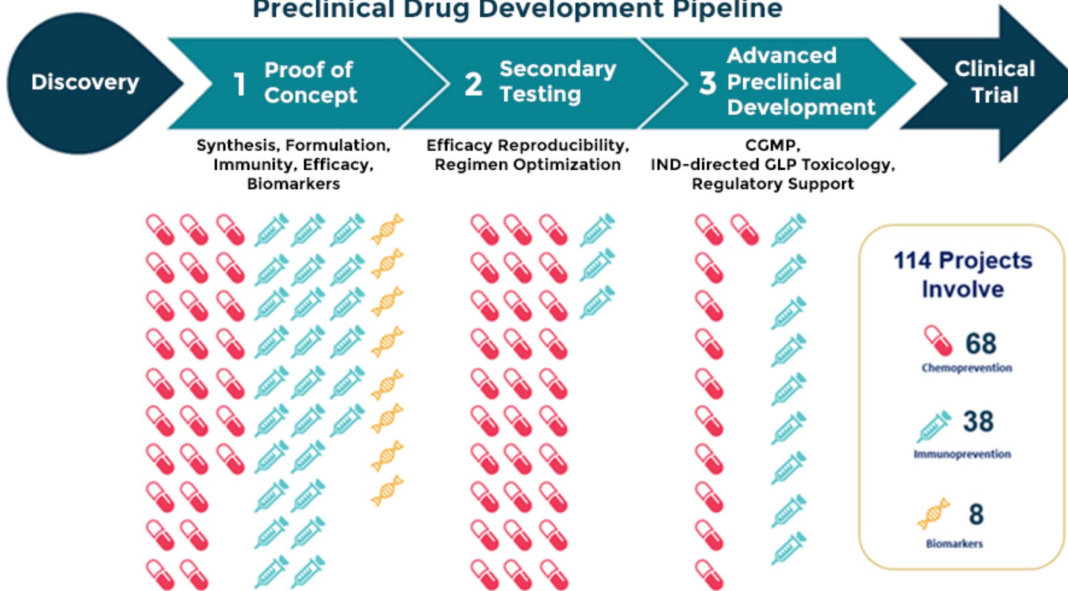
- **Immunotherapy is now being studied as a potential way to help prevent cancer. Where does this research stand?**

- **Immunotherapy** has been a great advance for cancer treatment. So this "immunoprevention" research is essentially looking at whether we can harness the immune system as a form of cancer surveillance, to detect and snuff out cells with the earliest changes that will lead to cancer.
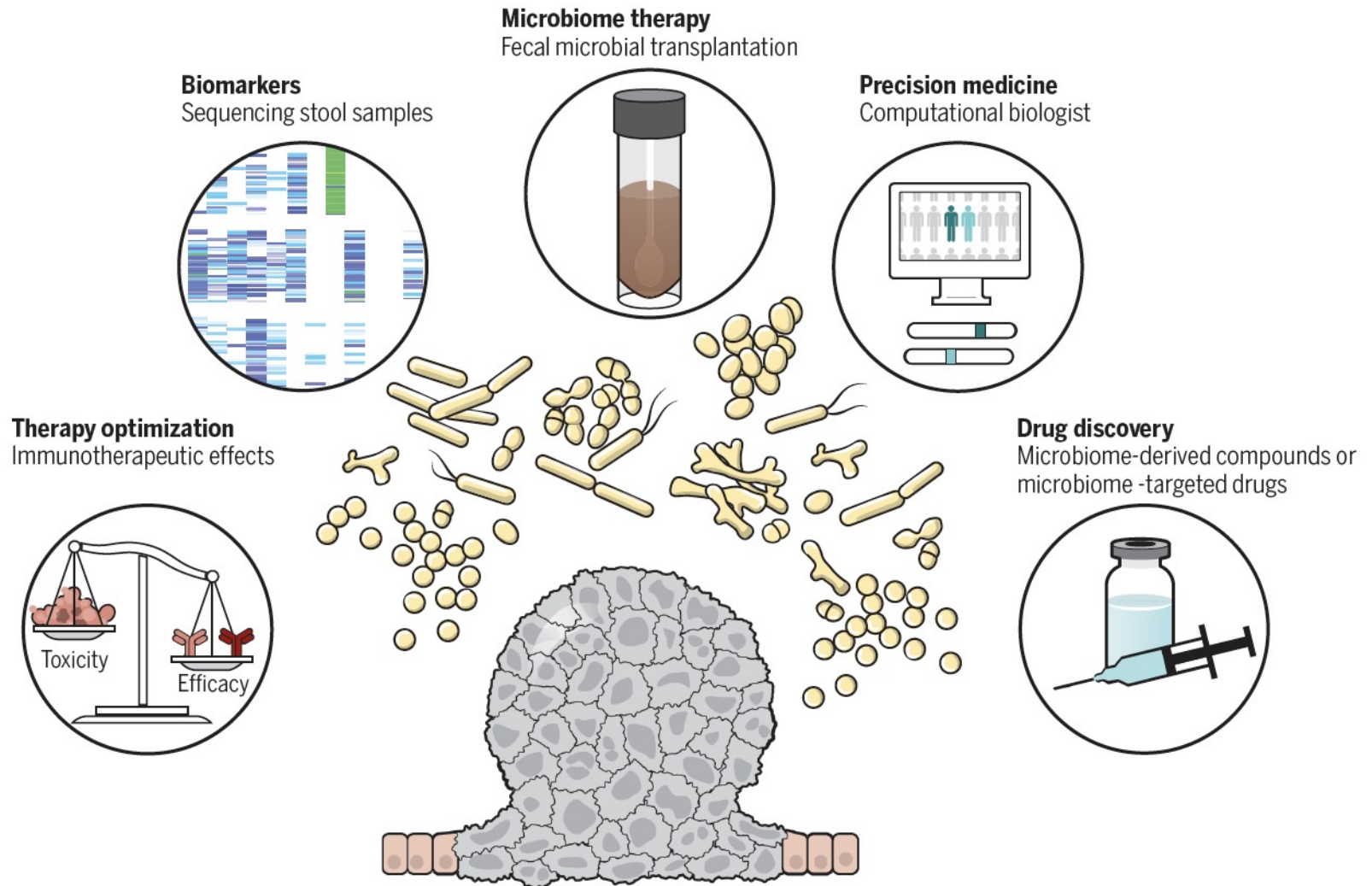
- A new initiative to promote the discovery of preventive therapies, and that will include some **immunoprevention drugs**. In particular, we're expanding activities around developing preventive agents for those at high risk for cancer, such as those with a genetic predisposition like Lynch syndrome. The idea is to start this work with a focus on the highest-risk groups.

The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies

Biomarkers
Sequencing stool samples

Microbiome therapy
Fecal microbial transplantation

Precision medicine
Computational biologist

Therapy optimization
Immunotherapeutic effects

Toxicity

Efficacy

Drug discovery
Microbiome-derived compounds or microbiome -targeted drugs

Zitvogel, *Science 359*:1366, 2018

- **Diet and exercise** are areas of intense interest in cancer prevention. **Where do you think these two areas fit into the overall prevention picture?**

- The thought is definitely out there that if you eat this specific thing or avoid this other thing, you'll prevent cancer. Unfortunately, no specific foods or activities are proven to prevent cancer, except perhaps avoiding cooked red meat, and there are numerous factors that make research to identify such factors difficult to do.

- We know that obesity increases the risk for about 13 cancers. And we know that a healthy lifestyle, including weight management, will likely reduce your cancer risk. Of course, not everyone has equal access to healthy foods and things that promote healthy behaviors and much of that is influenced by policy matters.

Healthy Living Is the Best Revenge

Findings From the European Prospective Investigation Into Cancer and Nutrition–Potsdam Study

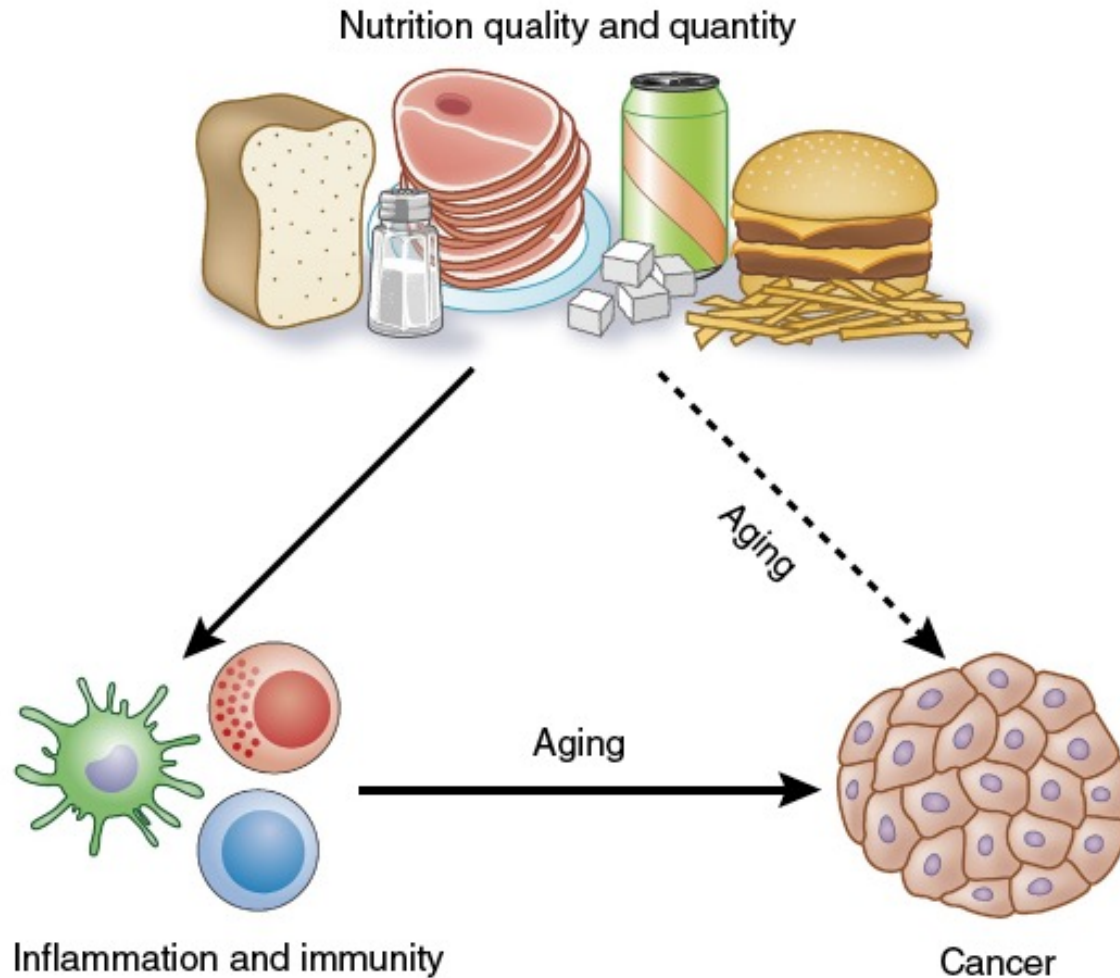- ✓ **4 Factors Reduce Risk of Developing Chronic Disease by 78% and Cancer by 36%**

- ✓ **Have a Body Mass Index < 30**

- ✓ **Never Smoke**

- ✓ **Perform 3.5 h/wk or more Physical Exercise**

- ✓ **Adhere to Healthy Dietary Principles (High Intake of Fruits, Vegetables, Whole-Grain Bread and Low Meat Consumption)**

Dietary Chemoprevention:
The missing ingredient
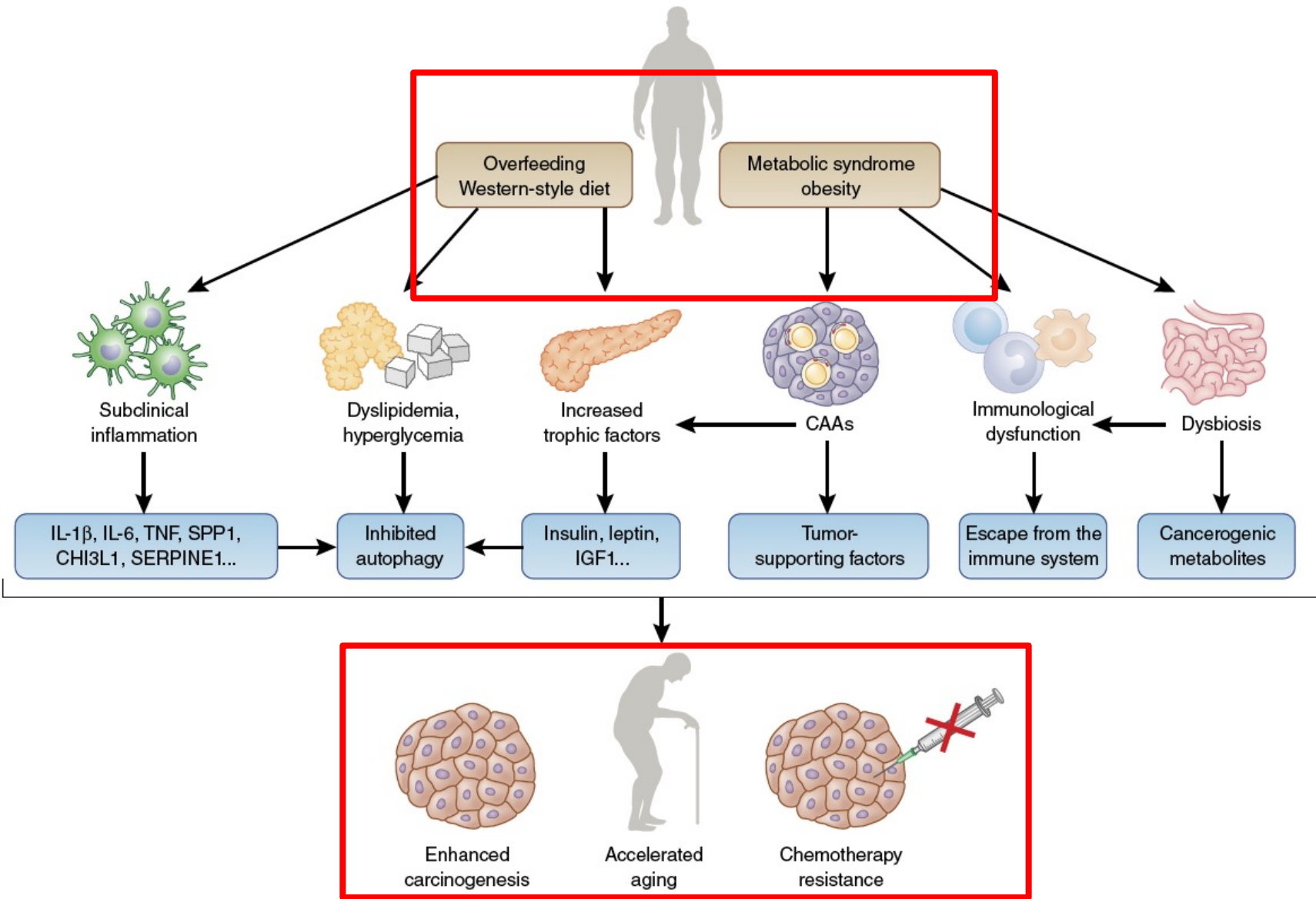

Human Malignancies are linked to:

35% to diet, 14-20% to obesity

Coussens, L.M., *Science 339*:286, 2013

Nutrition, inflammation and cancer

Nutrition quality and quantity

Aging

Aging

Inflammation and immunity

Cancer

Nutrition, inflammation and cancer

Zitvogel, *Nature Immunol 18*:843, 2017

Martucci, *Nutr Rev 75*:442, 2017
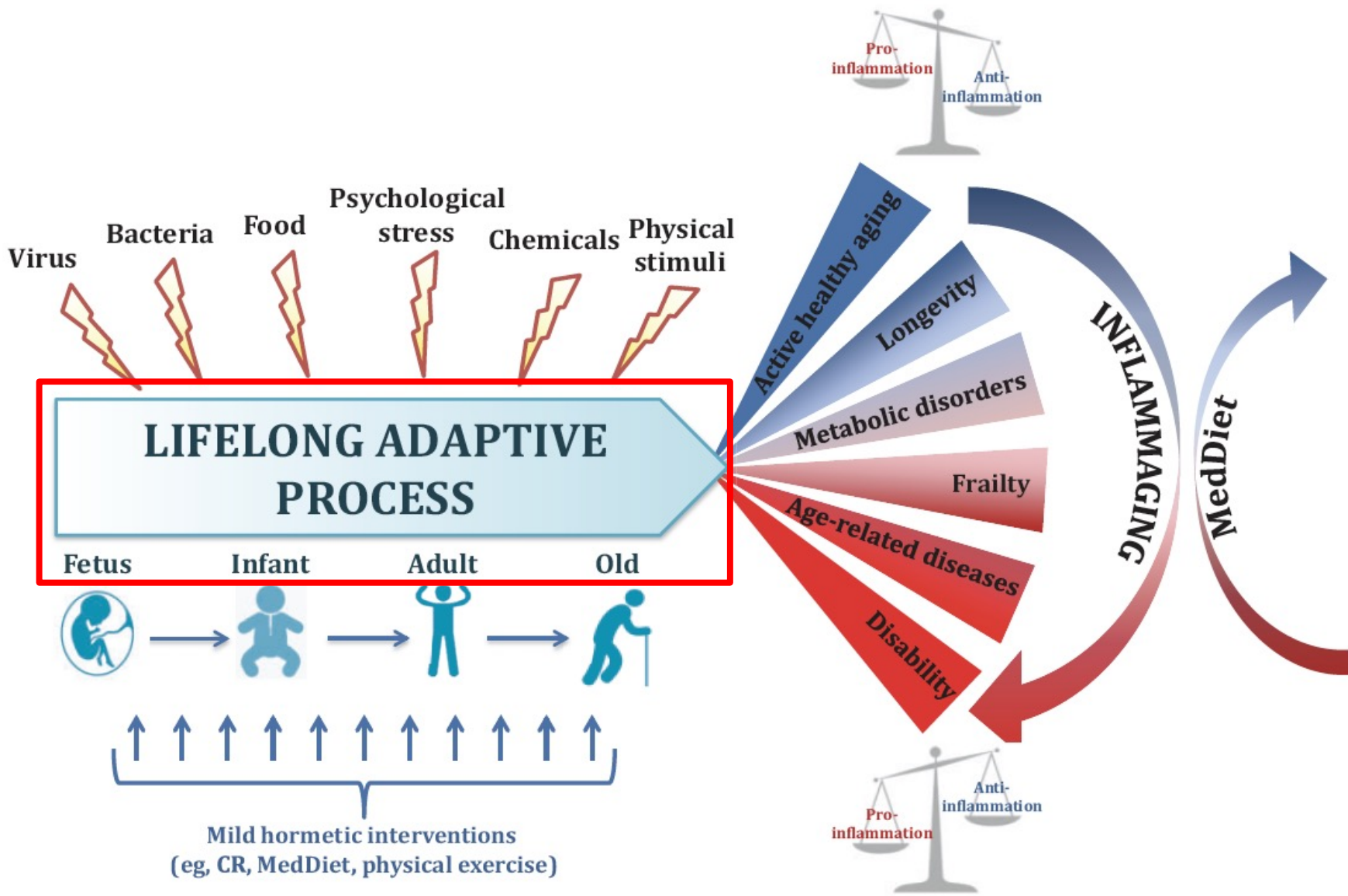
Also PRETTY SURE that Intentional Weight Loss Reduces Risk for Several Cancers
…at least among <u>adult</u> women and for obesity-related cancers

0.81
Breast Cancer

0.91
Colon Cancer

0.96
Endometrial Cancer

0.96
Obesity-Related Cancers: Breast, colon, endometrial & kidney

0.0   0.2   0.4   0.6   0.8   1.0   1.2   1.4
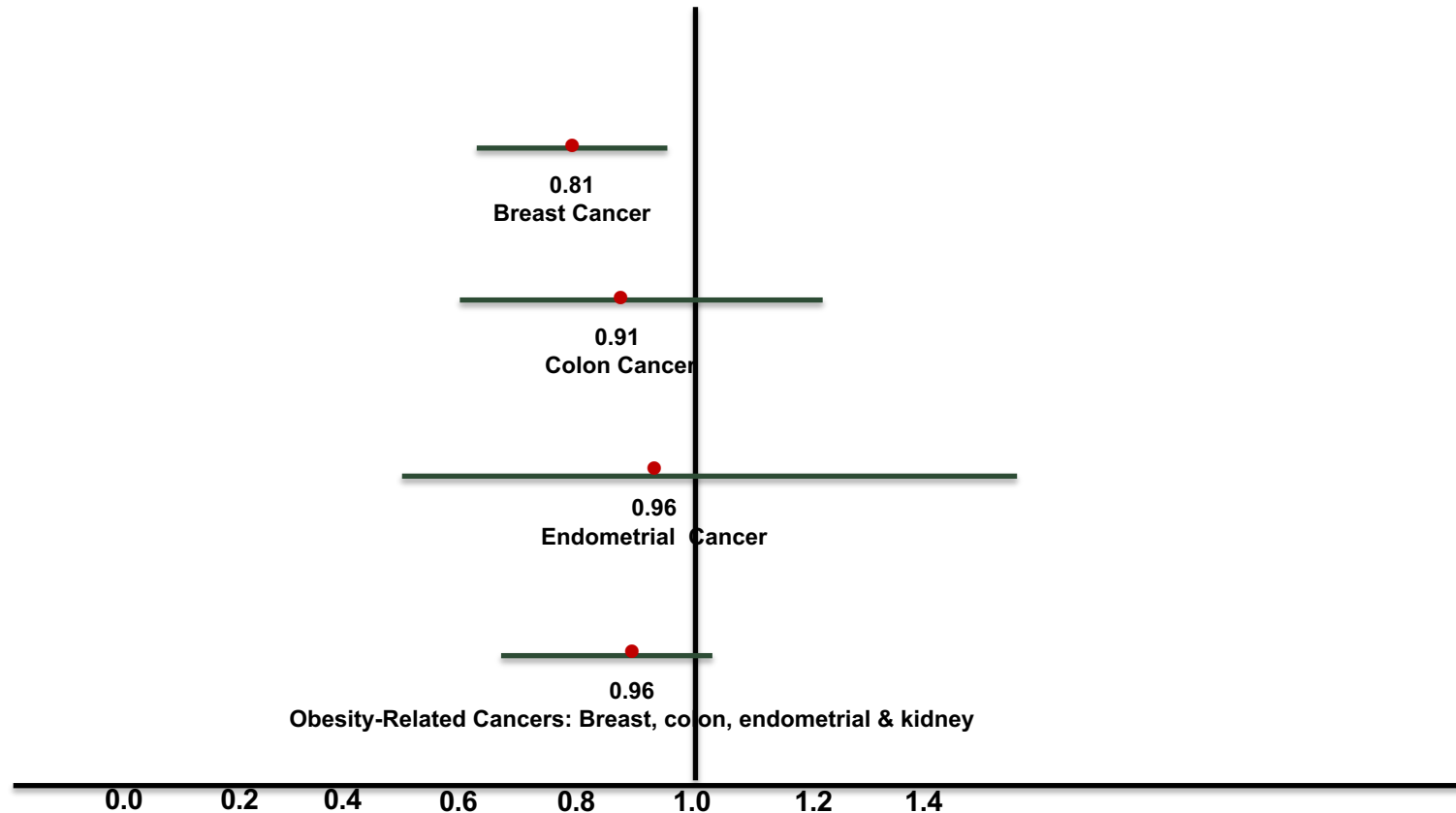
Parker, *Intl J Obes Relat Metab Dis* **27:1447, 2003**

Similar data Miyagi Cohort (>10,000 Japanese women) - **Kawai,** *Br J Cancer,* **Sept 2010**

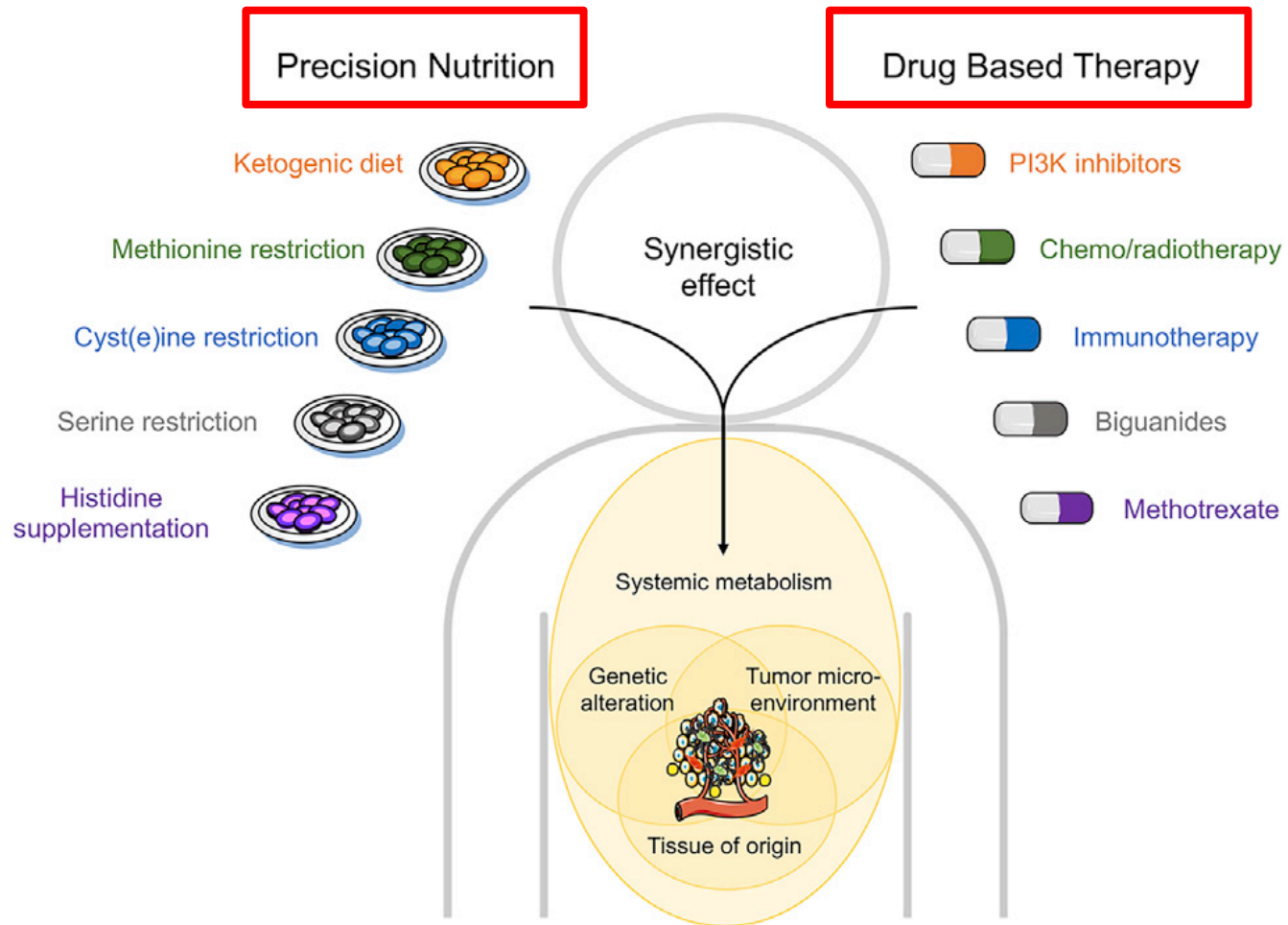# Dietary Approaches to Cancer Therapy

Figure 6. Rational Combinations of Diets and Drug-Based Therapies

Precision Prevention and Early Detection of Cancer: Fundamental Principles

Principle	Key concepts
Risk quantification	Identification of individuals who will maximally benefit from prevention or early-detection strategies based on genetic, molecular, and other biomarker information. Risk may be conferred by inheritance, existence of preneoplastic condition, or exposure.
Mechanistic foundation	An understanding of the basic biology of early carcinogenesis events, including genomic susceptibility, metabolic reprogramming, drivers of preneoplasia, the tumor microenvironment, immune modulation, and biomarkers that may define etiologic and risk heterogeneity.
Heterogeneity in phenotype and response	Preventive interventions or early-detection strategies may have different efficacy and toxicities in certain individuals based on their biological characteristics.

Principle	Key concepts
Timing	A prevention "sweet spot" may exist in terms of the timing of the preventive intervention or detection method. Optimal timing of preventive interventions or early-detection strategies requires a clear understanding of the etiologic window in which carcinogenic events are working.
Effective prevention modalities	Effective interventions including risk-reducing surgery to remove tissue at risk, exposure modification, vaccination including immunoprevention, chemoprevention, treatment or removal of premalignant lesions, screening and early-detection methods based on molecular events. The optimal application of these interventions may depend on an individual's underlying risk profile.
Consideration of unintended effects	Favorable risk-benefit ratios for patients and/or cost-benefit ratios to governments or insurers may exist. Some very high-risk individuals may accept more intensive/invasive extreme preventive strategies (that may confer higher levels of toxicity) that would not be acceptable to the general population.

NCI BUDGET FISCAL YEAR 2019

NCI BUDGET

OCTOBER 2018 ····► SEPTEMBER 2019

$5.74 BILLION

Note: NCI also received $400 million in FY 2019 for the Beau Biden Cancer Moonshot, which was authorized in the 21st Century Cures Act of 2016.

cancer.gov/about-nci/budget

✓ **Less than 1.5% of total biomedical research funding is devoted to prevention programs**

(Colditz, *Sci Transl Med 4*:127rv4, 2012; Ludwig, *Science 362*:764, 2018)

NCI Shady Grove
Home of the Division of Cancer Prevention

Advisor

Advisor Personal funding matches (5)	Deadline	Amount
new [Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT) Centers (U54 Clinical Trial Not Allowed)](#) National Institutes of Health (NIH) United States Department of Health and Human Services (HHS)	October 7, 2021 Confirmed	[see record](#)
new [Cancer Prevention-Interception Targeted Agent Discovery Program (CAP-IT) Data and Resource Coordination Center (CAP-IT DRCC) (U24 Clinical Trial Not Allowed)](#) National Institutes of Health (NIH) United States Department of Health and Human Services (HHS)	September 7, 2021 Confirmed	$240,000